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1. Your reference — P18722GB

2. Patent application number *(The Patent Office will fill in this part)* — 19 FEB 1998 — **9803536.3**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

JAMES BLACK FOUNDATION LIMITED
68 HALF MOON LANE
DULWICH
LONDON
SE24 9JE

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **UNITED KINGDOM** — 5583760001

4. Title of the invention — **HISTAMINE H_3 RECEPTOR LIGANDS**

5. Name of your agent *(if you have one)* — **Carpmaels & Ransford**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)* — **83001**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body

See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	**78**
Claim*(s)*	**8**
Abstract	
Drawing*(s)*	**7 + 7**

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels + Ransford — Date: **18th February 1998**

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mr. Adrian J. Fisher, Carpmaels & Ransford** — **0171 242 8692**

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HISTAMINE H_3 RECEPTOR LIGANDS

This invention relates to compounds which bind to histamine H_3 receptors, and to methods of making such compounds.

Histamine is well known as a mediator in certain hypersensitive reactions of the body, such as allergic rashes, hayfever and asthma. These conditions are now commonly treated with potent antagonists of histamine, so-called "antihistamines".

In the 1940s, it was noted that some physiological effects of histamine, such as increased gastric acid secretion and cardiac stimulation, were not blocked by the antihistamines which were then available. This led to the proposal that histamine receptors exist in at least two distinct types, referred to as H_1 and H_2 receptors. Subsequently, H_2 antagonists (such as cimetidine, ranitidine and famotidine) were identified, and they have become important in the treatment of gastric ulcers.

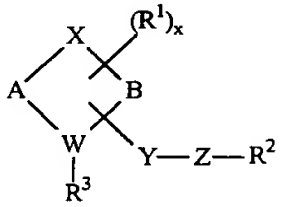
In the early 1980s, it was established that histamine also has a role as a neurotransmitter in the central nervous system. Arrang *et al.*, Nature 302, 832 to 837 (1983), proposed the existence of a third histamine receptor subtype (H_3) located presynaptically on histaminergic nerve endings. Arrang *et al.* postulated that the H_3 receptor is involved in inhibiting the synthesis and release of histamine in a negative feedback mechanism. The existence of the H_3 receptor was subsequently confirmed by the development of selective H_3 agonists and antagonists (Arrang *et al.*, Nature 327, 117 to 123 (1987)). The H_3 receptor has subsequently been shown to regulate the release of other neurotransmitters both in the central nervous system and in peripheral organs, in particular in the lungs and GI tract. In addition, H_3 receptors are reported to regulate the release of histamine from mast cells and enterochromaffin-like cells.

A need exists for potent and selective H_3 ligands (both agonists and antagonists) as tools in the study of the role of histamine as a neurotransmitter, and in its roles as a neuro-, endo- and paracrine hormone. It has also been anticipated that H_3 ligands will have therapeutic utility for a number of indications including use as sedatives, sleep regulators, anticonvulsants, regulators of hypothalamo-hypophyseal secretion, antidepressants and

modulators of cerebral circulation, and in the treatment of asthma and irritable bowel syndrome.

A number of imidazole derivatives have been proposed in the patent literature as H_3 ligands. Representative are the disclosures of EP-A-0197840, EP-A-0214058, EP-A-0458661, EP-A-0494010, EP-A-0531219, WO91/17146, WO92/15567, WO93/01812, WO93/12093, WO93/12107, WO93/12108, WO93/14070, WO93/20061, WO94/17058, WO95/06037, WO95/11894, WO95/14007, US-A-4988689 and US-A-5217986.

According to the present invention, there are provided compounds of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

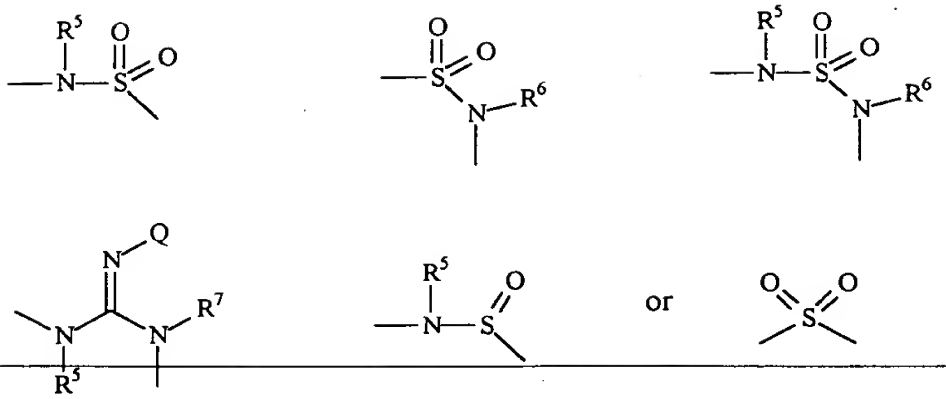
R^3 is absent when -Y-Z-R^2 is attached to W, or is C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

Y is C_2 to C_{10} alkylene and replaces a hydrogen atom on any of A, B, W and X; and

Z is



wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which one hydrogen atom may be replaced by halogen, and Q is H, methyl or -CN, or Q is linked to R^5 or R^7 to form a five-membered ring,

and pharmaceutically acceptable salts thereof.

In preferred compounds according to the invention, x is 0 or 1, and more preferably 0. R^1, when present, is preferably selected from hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

R^2 is preferably selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo. Particularly preferred groups for R^2 include phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, toluyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

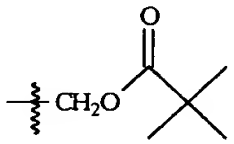
When -Y-Z-R^2 is not attached to W, R^3 is preferably C_1 to C_7 alkyl or benzyl.

R^5, R^6 and R^7 are preferably H, aryl(C_1 to C_3)alkyl or cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

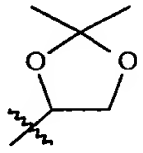
Y is preferably ethylene, propylene, butylene, pentylene , hexylene or heptylene.

The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", Drug Delivery Systems, pp. 112-176 (1985), and Drugs, 29, pp.455-473 (1985).

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-COOR^8$, wherein R^8 is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:



or



Amidated acid groups include groups of the formula $-CONR^9R^{10}$, wherein R^9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^{10} is -OH or one of the groups just recited for R^9.

Compounds of formula (I) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

The compounds of the invention may exist in various enantiomeric, diastereomeric and tautomeric forms. It will be understood that the invention comprehends the different enantiomers, diastereomers and tautomers in isolation from each other, as well as mixtures of enantiomers, diastereomers and tautomers.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups. The term "hydrocarbylene" refers to corresponding divalent groups, the two free valencies being on separate atoms.

When reference is made herein to a carbon atom of a hydrocarbyl group being replaced by O, S or N, it will be understood that what is meant is that a $-CH_2-$ group is replaced by –O- or –S-, or that a $\begin{array}{c}-\\ -CH-\\ |\end{array}$ group is replaced by a $\begin{array}{c}-\\ -N-\\ |\end{array}$ group.

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms, and which may be substituted. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above, which may be substituted.

A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring, and which may be substituted. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, halo, sulphamoyl and cyano.

The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

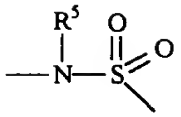
Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 μg/kg and 50 mg/kg, especially between 10 μg/kg and 10 mg/kg, eg. between 100 μg/kg and 2 mg/kg.

Compounds according to the invention wherein Z is

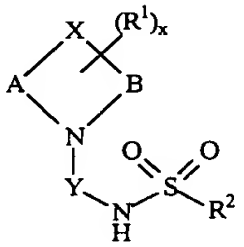


may be made by the reaction scheme which is illustrated in Figure 1.

In Figure 1, the amine (1) is reacted with a sulfonyl chloride (R^2SO_2Cl) in the presence of a base such as triethylamine, in a suitable solvent such as dichloromethane. A reaction of this type is described in greater detail below in Example 33.

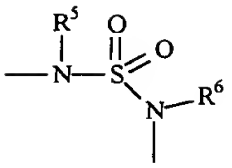
In Figure 1, and in a number of the other reaction schemes shown in the Figures, R^{3A} represents C_1 to C_7 hydrocarbyl or a suitable protecting group such as *tert*-butoxycarbonyl. If R^{3A} is a protecting group, it can be removed by conventional deprotection, and R^3 can then be introduced in the final stage by reductive amination of the secondary amine using an aldehyde of the form $R^{3B}CHO$ and sodium triacetoxyborohydride, wherein R^{3B} is a homolog of the desired R^3 group having one fewer carbon atoms in the carbon chain.

Compounds according to the invention which are of the form



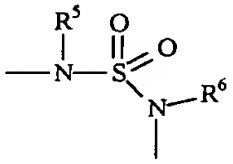
may be prepared by the reaction scheme which is depicted in Figure 2. In this scheme, the amino alcohol (2) is reacted with a sulfonyl chloride of the form R^2 to form compound (4). This reaction is conducted in the presence of a base such as triethylamine. A suitable solvent for the reaction is DCM. Compound (4) is then reacted with triphenylphosphine and carbon tetrachloride (preferably in a mixture with chloroform) to form the chloro derivative (5). This in turn is reacted with the cyclic imine (6) in a suitable solvent such as DCM to form the target compound (7). Further details of this reaction scheme are illustrated in Example 34 below.

Compounds wherein Z is



may be made by the scheme illustrated in Figure 3. Chlorosulfonyl isocyanate (CSI) is first reacted with *tert*-butanol in a suitable solvent such as DCM. The reaction product (8) is then reacted with the amine (1) in the presence of a base such as triethylamine (and preferably in DCM as solvent) to form the N-protected sulfamide (9). This is then reacted with sodium hydride and R^2Br in a solvent such as DMF to form compound (10). When the group R^5 in the target compound (11) is hydrogen, compound (10) is simply deprotected using a suitable reagent such as trifluoroacetic acid (TFA). Example 59 below illustrates the preparation of N-(4-chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide by this route. However, when the group R^5 in the target compound is other than hydrogen, compound (10) is first treated with R^5Br in the presence of a base to form compound (10A) before deprotection.

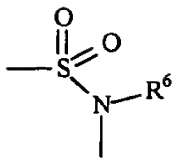
Figure 4 illustrates an alternative route for compounds wherein Z is



According to this scheme, compound (12) is reacted with the N-protected sulfamide (13) in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) in a suitable solvent such as THF. The resulting compound (14) is then deprotected in conventional fashion to provide the target compound (15), if the group R^6 in the target compound is hydrogen. If R^6 is not hydrogen, compound (14) is reacted with R^6Br in the presence of a base to form compound (14A) before the deprotection step. This reaction scheme is further illustrated by Example 60 below.

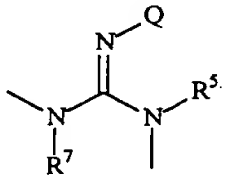
In some cases, the compound (15) may also be obtained by the reaction shown in Figure 5. In this procedure, which is exemplified in Example 87 below, the amine (1) is reacted with sulfamide (16) and an amine of the form R^2R^6NH.

Figure 6 illustrates a scheme for preparing compounds wherein Z is



In this scheme, Y^2 represents a bond or a C_1 to C_8 alkylene group. Dimethylsulfoxide is first added to oxalyl chloride (in a suitable solvent such as DCM) at reduced temperature. Compound (17), containing a free hydroxyl group, is then added, followed by a base such as triethylamine. The resulting aldehyde (18) is then reacted with the N-protected methyl sulfonamide (19) to yield compound (20). The N-protected methyl sulfonamide (19) is suitably prepared by reaction of an amine of the form R^2NH_2 with mesyl chloride, followed by *tert*-butoxycarbonyl protection. Compound (20) is then reduced (e.g. by hydrogenation in the presence of a palladium-on-charcoal catalyst) to form the target compound (21) in which R^6 is hydrogen. Example 88 below illustrates a synthesis by this route. If R^6 is to be other than hydrogen, compound (21) is reacted with R^6Br in the presence of a base to form compound (21A).

Figure 7 illustrates a scheme for preparing compounds wherein Z is



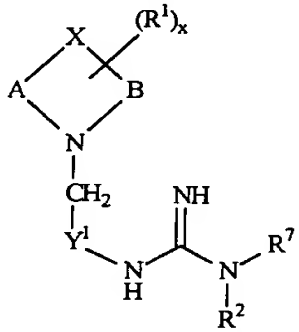
According to this scheme, the amine (1) is reacted with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) in a suitable solvent such as THF. The resulting N-protected guanidine (23) is then deprotected using any appropriate means, such as hydrogen chloride-dioxan, to yield the target compound (24) in which R^7 is hydrogen. If R^7 in the target compound is other than hydrogen, compound (23) is reacted with R^7Br in the presence of a base to yield compound (23A) before the deprotection step. An illustrative synthesis of this type is given below in Example 1.

Figure 8 illustrates a suitable route for the preparation of guanidine derivatives wherein R^2 is other than hydrogen. According to this scheme, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) is first reacted with sodium hydride (in a suitable solvent such as DMF), and then with a compound of the form R^2Br to

yield the guanidine derivative (25). This is then reacted with the amine (1), and subsequently deprotected, in a manner analogous to that shown in Figure 7. A preparation of this type is illustrated in Example 2 below.

Compound (25) may alternatively be derived from 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) by reaction with an alcohol of the form R^2OH in the presence of triphenylphosphine and DEAD, preferably in THF as solvent. This variation is illustrated in Example 3 below.

An alternative route for the preparation of compounds of the form



(in which Y^1 represents a C_1 to C_9 alkylene group) is illustrated in Figure 9. As shown in Figure 9, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) is reacted with an enol of the form $HO\text{-}Y^1\text{-}CH{=}CH_2$ in the presence of triphenylphosphine and DEAD. The resulting compound (26) is then reacted with $R^2R^7NH_2$ to provide compound (27), which is subsequently converted to the corresponding aldehyde (28) by treatment first with ozone and then with methylsulfide. Reaction of the aldehyde with the cyclic imine (29) in the presence of triacetoxyborohydride then affords the compound (30), from which the target compound (31) may be obtained by conventional deprotection methods. A synthesis of this type is illustrated in Example 14 below.

Compounds according to the invention in which Z is a sulfinamide moiety may be prepared by the reaction scheme illustrated in Figure 10. According to this scheme, the thiol compound R^2SH (32) is reacted with N-bromosuccinimide in methanol, to provide the sulfinic acid ester (33). This is then reacted with the amine (1) and lithium diisopropylamide to provide the target compound (34). Example 39 below provides further details of this preparative method.

Compounds in which Z is a sulfone group may be prepared by the method shown in Figure 11, in which Y^1 represents a C_1 to C_9 alkylene group. In this method, sodium hydride is added to the thiol compound R^2SH (32), followed by an appropriate ester (e.g. the ethyl ester) of an acid of the form Br-Y^1-COOH (35), to form the sulfanyl compound (36). This is then oxidised (e.g. with *meta*-chloroperoxybenzoic acid) to the corresponding sulfonyl compound (37). Appropriate reduction (e.g. with lithium aluminium hydride) then provides the alcohol (38), which in turn is oxidised to the aldehyde (39) using a reagent such as sulfur trioxide-pyridine. Finally, this is then reacted with the cyclic imine (6) under conditions analogous to those described above with reference to Figure 9. A synthesis of this type is illustrated in Example 40 below.

EXPERIMENTAL

^{1}H NMR were recorded on a Bruker DRX-300 at 300MHz and the chemical shifts were recorded relative to an internal standard and all coupling constants are reported in Hz. Flash column chromatography was performed on Merck silica gel 60 using reported solvent systems. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl under argon and distilled prior to use. Dichloromethane (DCM) was dried over calcium hydride and distilled prior to use. Commercially available anhydrous N,N-dimethylformamide (DMF) was used without further purification. Commercially available hydrogen chloride in dioxan (4M) was used to prepare hydrochloride salts as described. All reactions were carried out under a positive pressure of dry argon. All microanalysis are quoted as percentages.

Example 1

N-(3-Pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *N,N'-Bis(tert-butoxycarbonyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* A solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (580mg, 2.00mmol) and N-(3-aminopropyl)pyrrolidine (665mg, 5.19mmol) in THF (20ml) and water (2ml) heated at reflux for 1h. The solvent was evaporated at reduced pressure and the residue partitioned between ethyl acetate (50ml) and water (50ml). The aqueous was discarded and the organic washed with brine (50ml) and then dried over anhydrous sodium sulfate. The filtrate was evaporated and the residue purified by

flash column chromatography (silica 90:10:1 DCM:methanol:ammonia). The product was obtained as a colourless oil (718mg, 97%). ^{1}H NMR ($CDCl_3$) 11.49 (1H, bs), 8.72 (1H, bs), 3.54-3.48 (2H, m), 2.57-2.52 (6H, m), 1.79-1.72 (6H, m), 1.51 (9H, s), 1.50 (9H, s).

Step b *N-(3-Pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.*

To a solution of N,N'-bis(*tert*-butoxycarbonyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine (718mg, 1.94mmol) in dioxan (5ml) was added a solution of hydrogen chloride-dioxan (4M, 4ml, 16mmol). The resultant solution was stirred at ambient temperature for 16h to give a pink suspension. The solid was removed by filtration and dried *in vacuo* at 50°C. The solid was dissolved in aqueous hydrochloric acid (1M, 10ml) and the resultant solution heated at reflux for 1h. The solvent was removed at reduced pressure and the residue evaporated from ethanol (10ml), chloroform (10ml) and ether (10ml) to give the title compound as a white foam. ^{1}H NMR (DMSO-d_6) 11.04 (1H, bs), 8.00 (1H, t, 6), 7.54-7.12 (4H, bm), 3.53-3.39 (2H, m), 3.28-3.21 (2H, m), 3.16-3.09 (2H, m), 3.01-2.93 (2H, m), 2.00-1.86 (6H, m). Microanalysis found C 37.78 H 8.44 N 22.64. $C_8H_{20}Cl_2N_4.0.48H_2O$ requires C 38.16 H 8.39 N 22.25

Example 2

N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea.*

To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.00g, 3.45mmol) in DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 167mg, 4.18mmol) in a single portion. The resultant suspension was stirred at this temperature for 1h and then treated in a single portion with 4-chlorobenzylbromide (780mg, 3.80mmol). The cooling bath was removed and the reaction mixture stirred at ambient temperature for 16h. Water (50ml) was added and the aqueous extracted with ethyl acetate (50ml). The aqueous was discarded and the organic washed twice with brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (silica 9:2 hexane:ethyl acetate) to give the title compound as a colourless oil (987mg, 69%). ^{1}H NMR ($CDCl_3$) 7.30 (4H, s), 4.74 (2H, s), 2.31 (3H, s), 1.53 (9H, s), 1.42 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 2 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.27 (4H, bs), 4.78 (2H, s), 3.16 (2H, m) 2.43-2.37 (6H, bs), 1.76 (4H, m), 1.57-1.50 (2H, m), 1.50 (9H, s), 1.43 (9H, s).

Step c *N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* A solution of N,N'-bis(*tert*-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine (1.14g, 2.00mmol) in dioxan (5ml) was treated with hydrogen chloride-dioxan (15ml) and the reaction mixture stirred at ambient temperature for 16h. The solvent was evaporated at reduced pressure. The residue evaporated from DCM (30ml) to give the title compound as a foam (700mg, 95%). ^{1}H NMR (DMSO-d_6) 10.97 (1H, bs), 8.29 (1H, bs), 8.07 (1H, t, 6), 7.69 (2H, bs), 7.40 (2H, d, 8.4), 7.30 (2H, d, 8.4), 4.37 (2H, s), 3.48-3.45 (2H, m), 3.24-3.20 (2H, m), 3.08-3.03 (2H, m), 2.94-2.91 (2H, m), 2.00-1.84 (6H, m). Microanalysis found C 48.91 H 6.95 N 14.99. $C_{15}H_{25}Cl_3N_4$ requires C 48.99 H 6.85 N 15.24.

Example 3

N-(4-Methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-methoxybenzyl)-2-methyl-2-thiopseudourea.* To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.45g, 5.00mmol), 4-methoxybenzylalcohol (759mg, 5.50mmol) and triphenylphosphine (1.97g, 5.50mmol) in THF (20ml) was added diethylazodicarboxylate (1.286ml, 5.50mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue purified by flash column chromatography (90:10 hexane:ethylacetate) to give the title compound as a colourless oil (1.105g, 54%). ^{1}H NMR ($CDCl_3$) 7.30-7.27 (2H, m), 6.87-6.84 (2H, m), 4.71 (2H, s), 3.80 (3H, s), 2.27 (3H, s), 1.53 (9H, s), 1.44 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-methoxybenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 3 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10.00-9.50 (1H, bs), 7.27-7.22 (2H, m), 6.82-6.80 (2H, m), 4.73 (2H, s), 3.77 (3H, s), 3.09 (2H, bs), 2.40 (4H, bs), 2.31 (2H, bm), 1.73 (4H, s), 1.49 (9H, s), 1.42 (9H, s).

Step c *N-(4-Methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 3 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.00 (1H, bs), 8.25 (1H, bs), 8.11 (1H, t, 6), 7.71 (2H, bs), 7.29 (2H, d, 8.4), 6.93 (2H, d, 8.4), 4.36 (2H, s), 3.73 (3H, s), 3.55-3.26 (4H, m), 3.07 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 49.30 H 8.19 N 14.17. $C_{16}H_{28}Cl_2N_4O$-$1.5H_2O$ requires C 49.23 H 8.00 N 14.35.

Example 4

N-(2-Naphthalenemethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(2-naphthalenemethyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with 2-(bromomethyl)naphthalene replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.82 (4H, m), 7.48 (3H, m), 4.95 (2H, s), 2.29 (3H, s), 1.54 (9H, s), 1.42 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-naphthalenemethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product of Example 4 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 9.6 (1H, bs), 7.82-7.76 (4H, m), 7.49-7.44 (3H, m), 4.98 (2H, s), 3.14 (2H, m), 2.40 (4H, bs), 2.27 (6H, m), 1.68 (4H, m), 1.52 (9H, s), 1.45 (9H, s).

Step c *N-(2-Naphthalenemethyl)-N'(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 4 step b replacing the product from Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.00 (1H, bs), 8.39 (1H, bs), 8.13 (1H, bs), 7.94-7.85 (4H, m), 7.75 (2H, bs), 7.53-7.46 (3H, m), 4.62 (2H, d, 6), 3.48-3.32(4H, m), 3.08-3.06 (2H, m), 2.87 (2H, s), 1.93-1.84 (6H, m). Microanalysis found C 56.89 H 7.60 N 13.95. $C_{17}H_{28}Cl_2N_4$-H_2O requires C 56.86 H 7.53 N 13.96.

Example 5

N-(4-(Trifluoromethyl)benzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-(trifluoromethyl)benzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with α'-

bromo- α , α , α -trifluoroxylene replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.61 (2H, d, 8.1), 7.48 (2H, d, 8.1), 4.82 (2H, s), 2.33 (3H, s), 1.53 (9H, s), 1.41 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-(trifluoromethyl)benzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 5 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, bs), 7.57 (2H, d, 8.1), 7.46 (2H, d, 8.1), 4.86 (2H, s), 3.21 (2H, bs), 2.46-2.41 (6H, bs), 1.76 (4H, bs), 1.62 (2H, bs), 1.49 (9H, s), 1.41 (9H, s).

Step c *N-(4-(Trifluoromethyl)benzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 5 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.06 (1H, bs), 8.47 (1H, bs), 8.21-8.18 (1H, bm), 7.77-7.73 (4H, m), 7.57 (2H, d, 9), 4.58 (2H, d, 6), 3.49-3.44(4H, m), 3.35-3.29 (2H, m), 3.13-3.07 (2H, m), 2.94 (2H, bs), 1.96-1.88 (6H, m). Microanalysis found C 52.24 H 6.92 N 15.41. $C_{16}H_{25}Cl_2N_4F_3$ C 52.53 H 6.89 N 15.31.

Example 6

N-(4-Iodobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-iodobenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with 4-iodobenzylbromide replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.67-7.64 (2H, m), 7.19-7.09 (2H, m), 4.70 (2H, s), 2.31 (3H, s), 1.52 (9H, s), 1.37 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-iodobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product of Example 6 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR $CDCl_3$ 10-9.5 (1H, bs), 7.63 (2H, d, 8.1), 7.09 (2H, d, 8.1), 4.74 (2H, s), 3.46 (2H, bs), 2.46-2.38 (6H, m), 1.76 (4H, bs), 1.59 (2H, bs), 1.49 (9H, s), 1.42 (9H, s).

Step c *N-(4-Iodobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 6 step b replacing the product from Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.04 (1H, bs), 8.32 (1H, bs), 8.13 (1H, t, 6), 7.75-7.72 (4H, m), 7.17 (2H, d, 9), 4.41 (2H, d, 6), 3.49-3.44(2H, m), 3.31-3.29 (2H, m), 3.09-3.06 (2H, m), 2.93-2.92 (2H, bm), 1.97-

1.86 (6H, m). Microanalysis found C 34.05 H 6.14 N 10.42. $C_{15}H_{25}Cl_2N_4I$-$4H_2O$ C 33.91 H 6.26 N 10.55.

Example 7 *N-(3-Bromo-4-methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.*

Step a *3-Bromo-4-methoxybenzylalcohol.* To an ice-cooled solution of 3-bromo-4-methoxybenzaldehyde (2.15g, 10.0mmol) in THF (30ml) was added dropwise a solution of lithium aluminium hydride (1.0M in THF, 10ml, 10.0mmmol). The reaction mixture was stirred at this temperature for 15 minutes followed by 30 mins at ambient temperature. The reaction mixture was recooled with ice and treated dropwise with aqueous sodium hydroxide (2.0M, 2.0ml) and then diluted with diethyl ether. The resultant suspension was filtered through a pad of celite and the filtrate washed with brine (30ml) and dried over magnesium sulfate. The filtrate was evaporated at reduced pressure to give the title compound as a colourless oil (1.79g, 82 %). ^{1}H NMR ($CDCl_3$) 7.55 (1H, d, 2.1), 7.27-7.24 (1H, m), 6.89 (1H, d, 8.4), 4.50 (2H, d, 5.4), 3.39 (3H, s).

Step b *1,3'-Bis(tert-butoxycarbonyl)-1-(3-bromo-4-methoxybenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with the product of Example 7 step a replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 7.55 (1H, d, 2.1), 7.31-7.27 (1H, m), 6.87 (1H, d, 8.7), 4.68 (2H, s), 3.89 (3H, s), 2.31 (3H, s), 1.53 (9H, s), 1.44 (9H, s).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(3-bromo-4-methoxybenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product of Example 7 step b replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10-9.5 (1H, bs), 7.52 (1H, bs), 7.27-7.24 (1H, m), 6.84 (1H, d, 8.4), 4.72 (2H, s), 3.87 (3H, s), 3.15 (2H, bs), 2.41-2.36 (6H, bm), 1.74 (4H, bs), 1.52 (2H, bs), 1.51 (9H, s), 1.45 (9H, s).

Step d *N-(3-Bromo-4-methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 7 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 8.28 (1H, bs), 8.07 (1H, t, 6), 7.70 (2H, bs), 7.58 (1H, d, 2.1), 7.36-7.33 (1H, m), 7.12 (1H, d, 8.4), 4.37 (2H, s), 3.83 (3H, s), 3.48-3.29 (4H, m), 3.10-3.08 (2H, m), 2.96-2.93 (2H, s), 1.97-1.84 (6H, m). Microanalysis found C 43.09 H 6.33 N 12.38. $C_{16}H_{27}Cl_2N_4OBr$ requires C 43.45 H 6.15 N 12.67.

Example 8

N-Benzyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-benzyl-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with benzylbromide replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.37-7.28 (5H, m), 4.79 (2H, s), 2.29 (3H, s), 1.53 (9H, s), 1.41 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N''-benzyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 8 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.31-7.30 (5H, m), 4.81 (2H, s), 3.13 (2H, m) 2.42-2.35 (6H, bs), 1.48 (6H, m), 1.51 (9H, s), 1.44 (9H, s).

Step c *N-Benzyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* A solution of N,N'-bis(*tert*-butoxycarbonyl)-N'-benzyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine (1.89g, 4.11mmol) in ethanol (40ml) was treated with hydrochloric acid (2M, 40ml) and the reaction mixture heated at reflux for 1.5h. The solvent was evaporated at reduced pressure. The residue was evaporated from methanol (30ml) followed by DCM (30ml) and diethyl ether (30ml) to give the title compound as a foam (1.21g, 96%). ^{1}H NMR (DMSO-d_6) 11.10 (1H, bs), 8.36 (1H, bs), 8.16 (1H, s), 7.76 (2H, bs), 7.39-7.26 (5H, m), 4.37 (2H, d, 6), 3.47-3.27 (4H, m), 3.10-2.92 (4H, m), 1.96-1.86 (6H, m). Microanalysis found C 54.09 H 7.90 N 16.71. $C_{15}H_{26}Cl_2N_4$ requires C 54.05 H 7.86 N 16.81.

Example 9

N-(4-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-bromobenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with 4-bromobenzylbromide replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.45 (2H, d, 8.4), 7.22 (2H, d, 8.4), 4.72 (2H, s), 2.31 (3H, s), 1.53 (9H, s), 1.42 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-bromobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 9 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.48 (2H, d, 8.1), 7.24 (2H, d, 8.1), 4.47 (2H, s), 3.07 (2H, bs) 2.36-2.27 (6H, m), 1.65-1.52 (6H, m), 1.39 (9H, s), 1.35 (9H, s).

Step c *N-(4-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 8 step c with the product from Example 9 step b replacing the product from Example 8 step b. ^{1}H NMR (DMSO-d_6) 10.92 (1H, bs), 8.26 (1H, bs), 8.03 (1H, bs), 7.68 (2H, bs), 7.56 (2H, d, 9), 7.28 (2H, d, 9), 4.40-4.42 (2H, m), 3.52-3.46 (2H, m), 3.37-3.10 (2H, m), 3.11-2.94 (4H, m), 1.93-1.86 (6H, m). Microanalysis found C H N. $C_{15}H_{25}BrCl_2N_4$ requires C 43.71 H 6.11 N 13.59

Example 10

N-(3-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(3-bromobenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with 3-bromobenzylbromide replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.55-7.18 (4H, s), 4.74 (2H, s), 2.33 (3H, s), 1.53 (9H, s), 1.41 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(3-bromobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product of Example 10 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10.0-9.00 (1H, bs), 7.48-7.16 (4H, m), 4.78 (2H, s), 3.12 (2H, bs) 2.49 (6H, bs), 1.78-1.62 (6H, m), 1.51 (9H, s), 1.44 (9H, s).

Step c *N-(3-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product from Example 10 step b replacing the product from Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 8.32 (1H, bs), 8.08 (1H, bs), 7.72 (2H, bs), 7.55-7.47 (2H, m), 7.35-7.29 (2H, m), 4.45-4.44 (2H, m), 3.47-3.30 (4H, m), 3.13-3.08 (2H, bs), 2.96 (2H, bs), 1.94-1.87 (6H, m). Microanalysis found C 38.59 H 6.72 N 12.06. $C_{15}H_{25}BrCl_2N_4$-$3H_2O$ requires C 38.64 H 6.70 N 12.02.

Example 11

N-(2-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(2-bromobenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 2 step a with 2-bromobenzylbromide replacing 4-chlorobenzylbromide. ^{1}H NMR ($CDCl_3$) 7.56-7.53 (1H, m), 7.43-7.40 (1H, m), 7.34-7.27 (1H, m), 7.14-7.12 (1H, m), 4.88 (2H, s), 2.36 (3H, s), 1.54 (9H, s), 1.39 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-bromobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 11 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10.0-9.00 (1H, bs), 7.55-7.10 (4H, m), 4.92 (2H, s), 3.25 (2H, m) 2.47 (6H, bs), 1.78-1.54 (6H, m), 1.50 (9H, s), 1.43 (9H, s).

Step c *N-(2-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 11 step b replacing the product from Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.11 (1H, bs), 8.17 (2H, bs), 7.79 (2H, bs), 7.67-7.64 (1H, m), 7.43-7.25 (3H, m), 4.53-4.44 (2H, m), 3.50-3.45 (2H, m), 3.31 (2H, m), 3.17-3.11 (2H, m), 2.99-2.95 (2H, m), 1.97-1.88 (6H, m). Microanalysis found C 38.46 H 6.42 N 12.10. $C_{15}H_{25}BrCl_2N_4$-$3H_2O$ requires C 38.64 H 6.70 N 12.02.

Example 12

N-(4-Phenylbenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-phenylbenzyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-biphenylmethanol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 7.63-7.33 (9H, m), 4.85 (2H, s), 2.34 (3H, s), 1.56 (9H, s), 1.45 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-phenylbenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product of Example 12 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR $CDCl_3$ 10.0-9.00 (1H, bs), 7.60-7.31 (9H, m), 4.86 (2H, s), 3.17 (2H, bs), 2.40 (6H, bs), 1.73 (6H, s), 1.52 (9H, s), 1.46 (9H, s).

Step c *N-(4-Phenylbenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride salt.* The title compound was prepared as in Example 2 step c with the product of Example 12 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 8.33 (1H, bs), 8.1 (1H, bs), 7.75 (2H, bs), 7.69-7.65 (4H, m), 7.49-7.36 (5H, m), 4.49 (2H, m), 3.50-3.46 (2H, m), 3.32 (2H, m), 3.14-3.09 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 56.80 H 7.87 N 12.88. $C_{21}H_{30}Cl_2N_4$-$2H_2O$ requires C 56.63 H 7.69 N 12.58.

Example 13

N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(2-pyrrolidin-1-yl-ethyl)-guanidine.* The title compound was prepared as in Example 2 step b with N-(2-aminoethyl)pyrrolidine replacing N-(3-aminopropyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 7.28 (4H, s), 4.82 (2H, bs), 3.19 (2H, m) 2.43 (6H, bs), 1.76-1.74 (4H, m), 1.51 (9H, s), 1.44 (9H, s).

Step b *N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 8 step c with the product of Example 13 step a replacing the product of Example 8 step b. ^{1}H NMR (DMSO-d_6) 11.03 (1H, bs), 8.47 (1H, bs), 8.21 (1H, bs), 7.87 (2H, bs), 7.54-7.28 (4H, m), 4.49 (2H, d, 6), 3.68-3.30 (6H, m), 3.05-2.99 (2H, m), 2.01-1.87 (4H, m). Microanalysis found C 46.84 H 6.62 N 15.72. $C_{14}H_{23}Cl_3N_4$-0.25H_2O requires C 46.94 H 6.61 N 15.64.

Example 14

N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(1-pent-4-enyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-penten-1-ol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 5.88-5.74 (1H, m), 5.08-4.97 (2H, m), 3.54-3.49 (2H, m), 2.39 (3H, s), 2.11-2.04 (2H, m), 1.83-1.70 (2H, m), 1.51 (9H, s), 1.49 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-pent-4-enyl)-guanidine.* A solution of 1,3'-bis(*tert*-butoxycarbonyl)-1-(1-pent-4-enyl)-2-methyl-2-thiopseudourea (1.56g, 4.36mmol) and 4-chlorobenzylamine (1.20ml, 9.83mmol) in THF (20ml) and water (2ml) heated at reflux for 24h. The solution was diluted with ethyl acetate (30ml) and washed sequentially with water (30ml), aqueous citric acid (10%, 30ml) and brine (30ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (silica, 4:1 hexane:ethyl acetate) to give the title compound as colourless oil (1.464g, 74%). ^{1}H NMR ($CDCl_3$) 7.36-7.23 (4H, m), 5.82-5.73 (1H, m), 5.03-4.96 (2H, m), 4.40 (2H, bs), 3.68 (2H, bt, 7.2), 2.08-2.01 (2H, m), 1.68-1.54 (2H, m), 1.49 (9H, s), 1.48 (9H, s).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-butan-4-al)-guanidine.* Ozone gas was bubbled through a solution of N,N'-bis(*tert*-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-pent-4-enyl)-guanidine (500mg, 1.11mmol) in methanol (10ml) at -78^{0}C for 5 minutes. The blue solution was purged

of colour with nitrogen and then treated at this temperature with methylsulfide (0.81ml, 11.0mmol). The reaction mixture was allowed to warm to ambient temperature and stirred at this temperature for 2h. The solvent was evaporated at reduced pressure and the residue purified by flash column chromatography (silica 1:1 hexane:ethyl acetate) to give the title compound as an oil (403mg, 80%). ^{1}H NMR ($CDCl_3$) 9.75 (1H, s), 9.5 (1H, bs), 7.34 (2H, d, 8.4) 7.24 (2H, d, 8.4), 4.40 (2H, s), 3.70 (2H, t, 7.2), 2.48 (2H, t, 7.2), 1.93-1.83 (2H, m), 1.54 (9H, s), 1.49 (9H, s).

Step d *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine.* To an ice cooled suspension of N,N'-bis(*tert*-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-butan-4-al)-guanidine (400mg, 0.88mmol) and pyrrolidine (0.080ml, 0.96mmol) in 1,2-dichloroethane (3ml) was added in a single portion sodium triacetoxyborohydride (280mg, 1.32mmol). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (30ml) and extracted twice with ethyl acetate (20ml). The combined organics were dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to give the title compound as an oil (389mg, 87%). ^{1}H NMR ($CDCl_3$) 9.50 (1H, bs), 7.33 (2H, d, 7.8), 7.24 (2H, d, 7.8), 4.42-4.41 (2H, m), 3.68 (2H, m), 2.51 (6H, bs), 1.78 (4H, m), 1.69-1.55 (4H, m), 1.49 (9H, s), 1.48 (9H, s).

Step e *N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 8.26 (1H, bs), 8.03 (1H, bs), 7.64 (2H, m), 7.24 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.49-3.44 (2H, m), 3.20-3.16 (2H, m), 3.11-3.06 (2H, m), 2.95-2.91 (2H, m), 1.97-1.86 (4H, m), 1.73-1.63 (2H, m), 1.56-1.49 (2H, m).). Microanalysis found C 46.89 H 7.49 N 13.53. $C_{16}H_{27}Cl_3N_4$-0.61H_2O requires C 46.78 H 7.42 N 13.64.

Example 15

N-(4-Chlorobenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(1-hex-5-enyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 5-hexen-1-ol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 5.85-5.74 (1H, m), 5.05-4.94 (2H, m),

3.54-3.48 (2H, m), 2.39 (3H, s), 2.07 (2H, q, 7.2), 1.73-1.63 (2H, m), 1.51 (9H, s), 1.49 (9H, s), 1.45-1.37 (2H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-hex-5-enyl)-guanidine.* The title compound was prepared as in Example 14 step b with the product of Example 15 step a replacing the product of Example 14 step a. ^{1}H NMR ($CDCl_3$) 9.7 (1H, bs), 7.38-7.23 (4H, m), 5.81-5.69 (1H, m), 5.03-4.93 (2H, m), 4.41 (2H, bs), 3.67 (2H, bm), 2.08-2.01 (2H, m), 1.55-1.24 (22H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-pentan-4-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product of Example 15 step b replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 9.75 (1H, s), 9.5 (1H, bs), 7.34 (2H, d, 8.7) 7.24 (2H, d, 8.7), 4.41 (2H, s), 3.67 (2H, bs), 2.47-2.43 (2H, m), 1.63-1.56 (4H, m), 1.50 (9H, s), 1.48 (9H, s).

Step d *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(5-pyrrolidin-1-yl-pentyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product of Example 15 step c replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 9.50 (1H, bs), 7.36-7.23 (4H, m), 4.41-4.39 (2H, m), 3.68-3.63 (2H, m), 2.55-2.42 (6H, m), 1.81 (4H, bs), 1.70-1.48 (22H, m), 1.36-1.25 (2H, m).

Step e *N-(4-Chlorobenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product of Example 15 step d replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 8.28 (1H, bs), 8.00 (1H, bs), 7.64 (2H, m), 7.42 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.50-3.45 (2H, m), 3.20-3.13 (2H, m), 3.06-2.93 (4H, m), 1.97-1.86 (4H, m), 1.71-1.61 (2H, m), 1.53-1.43 (2H, m), 1.35-1.28 (2H, m). Microanalysis found C 48.33 H 7.59 N 13.30. $C_{17}H_{29}Cl_3N_4$-1.57H_2O requires C 48.15 H 7.64 N 13.21.

Example 16

N-(4-Chlorophenyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine.

Step a *N-(4-Chlorophenyl)-thiourea.* To stirred aqueous ammonia (880, 20ml) was added dropwise with ice-cooling a solution of 4-chlorophenylisothiocyanante (3.39g, 20.0mmol) in dioxan (20ml). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The solid was removed by filtration and the filtercake washed with water (50ml). The title compound was dried *in vacuo* (50^{0}C)

for 16h and isolated as a white solid (2.899g, 78%). ^{1}H NMR (DMSO-d_6) 9:72 (1H, bs), 7.61-7.32 (6H, bm).

Step b *1-(4-Chlorophenyl)-2-methyl-2-thiopseudourea hydroiodide.* To a solution of N-(4-chlorophenyl)-thiourea (2.82g, 15.11mmol) in acetone (30ml) was added iodomethane (1.41ml, 22.65mmol) and the resultant reaction heated at reflux for 1h. The solvent was removed at reduced pressure and the residue suspended in ethyl acetate (50ml). The solid was removed by filtration and the filter-cake washed with ethyl acetate (50ml) to give the title compound as a white solid (4.53g, 91%). ^{1}H NMR (DMSO-d_6) 11-9 (3H, bs), 7.57 (2H, d, 8.7), 7.36 (2H, d, 8.7), 2.68 (3H, s).

Step c *N-(4-Chlorophenyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine.* A solution of 1-(4-chlorophenyl)-2-methyl-2-thiopseudourea hydroiodide (986mg, 3.00mmol) and N-(3-aminopropyl)pyrrolidine (0.948ml, 7.50mmol) in ethanol (10ml) was heated at reflux for 16h. The solvent was removed at reduced pressure and the residue suspended in aqueous ammonia (880, 25ml). The solid was removed by filtration and the filter-cake washed sequentially with water (50ml) and diethyl ether (50ml) to give the title compound as a white solid (585mg, 69%). ^{1}H NMR (DMSO-d_6) 7.18-7.12 (2H, m), 6.76-6.66 (2H, m), 5.8-4.8 (3H, bs), 3.12 (2H, t, 6.9), 2.43-2.36 (6H, m), 1.69-1.56 (6H, m). Microanalysis found C 60.01 H 7.62 N 19.74. $C_{14}H_{21}ClN_4$ requires C 59.88 H 7.54 N 19.95

Example 17

N-(2-(4-Chlorophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(2-(4-chlorophenyl)ethyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-chlorophenethyl alcohol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 7.26 (2H, d, 8.4), 7.15 (2H, d, 8.4), 3.72-3.67 (2H, m), 2.98-2.93 (2H, m), 2.38 (3H, s), 1.58 (9H, s), 1.49 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 17 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.25 (2H, d, 8.4), 7.15 (2H, d, 8.4), 3.89-3.84 (2H, m), 3.20 (2H, m), 2.92-2.90 (2H, m), 2.52 (4H, m), 1.81-1.68 (4H, m), 1.50-1.47 (4H, m), 1.50 (9H, s), 1.47 (9H, s).

Step c *N-(2-(4-Chlorophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 8 step c with the product from Example 17 step b replacing the product from Example 8 step b. ^{1}H NMR (DMSO-d_6) 11.04 (1H, bs), 7.92 (1H, bs), 7.80 (1H, bs), 7.59 (2H, bs), 7.38-7.30 (4H, m), 3.50-3.23 (6H, m), 3.11-3.08 (2H, m), 2.98-2.92 (2H, m), 2.79 (2H, t, 7.5), 2.00-1.82 (6H, m). Microanalysis found C 50.31 H 7.17 N 14.41. $C_{16}H_{27}Cl_3N_4$ requires C 50.34 H 7.13 N 14.68.

Example 18

N-(3-(4-Chlorophenyl)propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(3-(4-chlorophenyl)propyl))-2-methyl-2-thiopseudourea.* To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (739mg, 3.00mmol) in DMF (5ml) was added sodium hydride (60% dispersion in mineral oil, 150mg, 3.75mmol) in a single portion. The resultant suspension was stirred at this temperature for 1h and then treated with a solution of 3-(4-chlorophenyl)propanemesylate (760mg, 3.06mmol). The cooling bath was removed and the reaction mixture stirred at 80^{0}C for 40h. Water (40ml) added and the aqueous extracted with ethyl acetate (40ml). The aqueous was discarded and the organic washed twice with brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (silica 5:1 hexane:ethyl acetate) to give the title compound as a colourless oil (664mg, 59%). ^{1}H NMR ($CDCl_3$) 7.28-7.25 (2H, m), 7.14-7.11 (2H, m), 3.56-3.50 (2H, m), 2.56-2.64 (2H, m), 2.39 (3H, s), 1.99-1.92 (2H, m), 1.52 (9H, s), 1.47 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(3-(4-chlorophenyl)propyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 18 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.22 (2H, d, 8.4), 7.10 (2H, d, 8.4), 3.63 (2H, t, 7.5), 3.35 (2H, bs) 2.62-2.57 (8H, bm), 1.82 (8H, m), 1.49 (9H, s), 1.45 (9H, s).

Step c. *N-(3-(4-Chlorophenyl)propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 18 step b replacing the product from Example 2 step b. ^{1}H

NMR (DMSO-d_6) 11.0 (1H, bs), 7.92 (2H, bs), 7.58 (2H, m), 7.32 (2H, d, 9), 7.24 (2H, d, 9), 3.49-3.47 (2H, m), 3.25 (2H, m), 3.17-3.12 (4H, m), 2.99-2.77 (2H, bm), 2.63 (2H, t, 7.5), 1.97-1.71 (8H, m). Microanalysis found C 51.28 H 7.43 N 13.84. $C_{17}H_{29}Cl_3N_4$ requires C 51.59 H 7.39 N 14.16.

Example 19

N-(4-Phenylbutyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(4-phenylbutyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-phenylbutan-1-ol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 7.30-7.25 (2H, m), 7.19-7.15 (3H, m), 3.56-3.51 (2H, m), 2.64 (2H, t, 7.2), 2.38 (3H, s), 1.72-1.56 (4H, m), 1.51 (9H, s), 1.47 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-phenylbutyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 19 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 7.29-7.25 (2H, m), 7.19-7.15 (3H, m), 3.66-3.46 (2H, bm), 3.32 (2H, bs), 2.65-2.55 (8H, m), 1.81 (6H, bs), 1.60 (4H, bs), 1.49 (9H, s), 1.45 (9H, s).

Step c *N-(4-Phenylbutyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product of Example 19 step b replacing the product from Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.07 (1H, bs), 7.92 (1H, bs), 7.84 (1H, bs), 7.57 (2H, bs), 7.29-7.13 (5H, m), 3.51-3.46 (2H, m), 3.28-3.26 (2H, m), 3.17-3.11 (4H, m), 2.98-2.96 (2H, m), 2.61-2.56 (2H, m), 1.97-1.84 (6H, m), 1.65-1.42 (4H, m). Microanalysis found C 52.70 H 8.77 N 13.43. $C_{17}H_{32}Cl_2N_4$-$2H_2O$ requires C 52.55 H 8.82 N 13.62.

Example 20

N-(2-(4-Chlorophenyl)ethyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine dihydrochloride.

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(2-pyrrolidin-1-yl-ethyl)-guanidine.* The title compound was prepared as in Example 17 step b with N-(2-aminoethyl)pyrrolidine replacing N-(3-aminopropyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 7.24 (2H, d, 8.4), 7.14 (2H, d, 8.4), 3.89 (2H, d, 7.8), 3.20 (2H, bs), 2.90 (2H, t, 7.8), 2.53 (6H, m), 1.80 (4H, m), 1.51 (9H, s), 1.47 (9H, s).

Step b *N-(2-(4-Chlorophenyl)ethyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 8 step c with the product from Example 20 step a replacing the product of Example 8 step b. ^{1}H NMR (DMSO-d_6) 10.97 (1H, bs), 7.94 (1H, bs), 7.86 (1H, bs), 7.68 (2H, bs), 7.38-7.31 (4H, m), 3.59-3.22 (8H, m), 3.00-2.99 (2H, m), 2.81 (2H, t, 6), 1.99-1.87 (4H, m). HRMS found 295.1699 and 297.1679 $C_{16}H_{27}Cl_3N_4$ requires.

Example 21

N-(2-(4-Chlorophenyl)ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-Chlorophenyl)ethyl)-N''-(1-pent-4-enyl)-guanidine.* The title compound was prepared as in Example 14 step b with 4-chlorophenethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 9.5 (1H, bs), 7.27 (2H, d, 7.5), 7.13 (2H, d, 7.5), 5.77-5.71 (1H, m), 5.03-4.96 (2H, m), 3.58 (2H, bs), 3.46 (2H, m), 2.88 (2H, bs), 2.00-1.95 (2H, m), 1.55-1.52 (2H, bm), 1.50 (9H, s), 1.46 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(1-butan-4-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 21 step a replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 9.73 (1H, s), 9.5 (1H, bs), 7.29-7.27 (2H, m) 7.20-7.14 (2H, m), 3.60 (2H, bs), 3.44 (2H, bs), 2.91-2.86 (2H, m), 2.40 (2H, t, 6.9), 1.75-1.67 (2H, m), 1.50 (9H, s), 1.46 (9H, s).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 21 step b replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 9.5 (1H, bs), 7.28 (2H, d, 8.4), 7.13 (2H, d, 8.4), 3.62-3.57 (2H, m), 3.48-3.42 (2H, m), 2.87 (2H, t, 6.9), 2.60-2.50 (6H, bm), 1.83 (4H, bs), 1.57-1.53 (4H, m), 1.50 (9H, s), 1.46 (9H, s).

Step d *N-(2-(4-Chlorophenyl)ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 21 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, bs), 7.81 (1H, bs), 7.69 (1H, bs), 7.51 (2H, m), 7.37 (2H, d, 8.7), 7.29 (2H, d, 8.7), 3.48-3.35 (4H, m), 3.14-3.06 (4H, m), 2.97-2.93 (2H, m), 2.78 (2H, t, 7.2), 2.00-1.87 (4H, m), 1.73-1.63 (2H, m), 1.53-1.43 (2H, m). Microanalysis found C 45.33 H 7.78 N 12.39. $C_{17}H_{29}Cl_3N_4$-$3H_2O$ requires C 45.39 H 7.84 N 12.45.

Example 22

N-(2-(4-Chlorophenyl)ethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(1-hex-5-enyl)-guanidine.* The title compound was prepared as in Example 15 step b with 4-chlorophenethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 9.50 (1H, bs), 7.28 (2H, d, 8.4), 7.12 (2H, d, 8.4), 5.82-5.73 (1H, m), 5.04-4.93 (2H, m), 3.58-3.56 (2H, bm), 3.45 (2H, bs), 2.87 (2H, t, 6.9), 2.06-1.99 (2H, m), 1.52-1.32 (22H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(1-pentan-4-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 22 step a replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 10-9.5 (1H, s), 9.5 (1H, t, 1.2), 7.29-7.26 (2H, m) 7.15-7.13 (2H, m), 3.59 (2H, t, 7.2), 3.45-3.44 (2H, m), 2.87 (2H, t, 7.2), 2.45-2.40 (2H, m), 1.58-1.40 (22H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-chlorophenyl)ethyl)-N''-(5-pyrrolidin-1-yl-pentyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 22 step b replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 9.60 (1H, bs), 7.29 (2H, d, 8.4), 7.12 (2H, d, 8.4), 3.60-3.41 (4H, m), 2.86 (2H, t, 6.9), 2.48-2.38 (6H, m), 1.78 (4H, bs), 1.50 (9H, s), 1.46 (9H, s), 1.53-1.38 (4H, m), 1.31-1.23 (2H, m).

Step d *N-(2-(4-Chlorophenyl)ethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 22 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 10.84 (1H, bs), 7.78 (1H, bs), 7.69 (1H, bs), 7.49 (2H, bs), 7.38-7.29 (4H, m), 3.51-3.37 (4H, m), 3.14-3.03 (4H, m), 2.98-2.90 (2H, m), 2.78 (2H, t, 7.2), 1.99-1.84 (4H, m), 1.72-1.62 (2H, m), 1.48-1.41 (2H, m), 1.36-1.29 (2H, m). Microanalysis found C 52.33 H 7.91 N 13.38. $C_{18}H_{31}Cl_3N_4$-requires C 52.75 H 7.62 N 13.67.

Example 23

N-(2-(1-Adamantane)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-((2-(1-adamantane)ethyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 2-adamantaneethanol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 3.58-3.53 (2H, m), 2.39 (3H, s), 1.95 (2H, bs), 1.73-1.43 (33, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(1-adamantane)ethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 23 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 3.64-3.59 (2H, bm), 3.33 (2H, bs), 2.54 (6H, m), 1.94-1.60 (16H, m), 1.51-1.47 (23H, m), 1.35-1.30 (2H, m).

Step c *N-(2-(1-Adamantane)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 8 step c with the product from Example 23 step b replacing the product of Example 8 step b. ^{1}H NMR (DMSO-d_6) 10.94 (1H, bs), 7.79 (1H, bs), 7.55 (1H, bs), 7.49 (2H, bs), 3.50-3.49 (2H, m), 3.30-3.24 (2H, m), 3.14-3.11 (4H, m), 2.9-2.94 (2H, m), 1.98-1.86 (9H, m), 1.70-1.58 (6H, m), 1.49-1.39 (6H, m), 1.32-1.27 (2H). Microanalysis found C 56.35 H 9.69 N 13.28. $C_{20}H_{38}Cl_2N_4$-H_2O requires C 56.73 H 9.52 N 13.23.

Example 24

N-(2-Cyclohexaneethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(2-cyclohexaneethyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with cyclohexaneethanol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 3.56-3.51 (2H, m), 2.39 (3H, s), 1.51 (9H, s), 1.48 (9H, s), 1.72-1.45 (7H, m), 1.27-0.89 (6H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-cyclohexaneethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 24 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 3.66-3.61 (2H, bm), 3.34 (2H, bs), 2.54 (4H, m), 1.89-1.40 (33H, m), 1.27-0.89 (6H, m).

Step c *N-(2-Cyclohexaneethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 24 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 10.92 (1H, bs), 7.78 (1H, bs), 7.64 (1H, bs), 7.49 (2H, bs), 3.50-3.46 (2H, m), 3.28-3.25 (2H, m), 3.14-3.12 (4H, m), 2.99-2.96 (2H, m), 1.98-1.86 (6H, m), 1.68-1.65 (5H, m), 1.47-1.09 (6H, m), 0.93-0.86 (2H, m). Microanalysis found C 49.49 H 10.18 N 14.44. $C_{16}H_{34}Cl_2N_4$-$2H_2O$ requires C 49.35 H 9.84 N 14.39.

Example 25

N-(Cyclohexanemethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(1-but-3-enyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 3-buten-1-ol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 5.82-5.71 (1H, m), 5.15-5.04 (2H, m), 3.61-3.56 (2H, m), 2.47-2.42 (2H, m), 2.40 (3H, s), 1.52 (9H, s), 1.49 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(1-but-3-enyl)-guanidine.* The title compound was prepared as in Example 14 step b with the product from Example 25 step a replacing the product of Example 14 step a and cyclohexylmethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 9.70 (1H, bs), 5.82-5.71 (1H, m), 5.12-5.03 (2H, m), 3.75 (2H, t, 7.2), 3.07-3.05 (2H, bm), 2.34-2.31 (2H, m), 1.77-1.58 (5H, m), 1.51 (9H, s), 1.47 (9H, s), 1.30-1.22 (4H, m), 0.97-0.89 (2H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(cylclohexanemethyl)-N''-(1-propan-3-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product of Example 25 step b replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 9.75 (1H, s), 9.5 (1H, bs), 3.98 (2H, t, 6.3), 3.00 (2H, d, 6), 2.78 (2H, t, 6.3), 1.78-1.59 (5H, m), 1.50 (9H, s), 1.47 (9H, s) 1.29-1.19 (4H, m), 0.98-0.94 (2H, m).

Step d *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 25 step c replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 9.50 (1H, bs), 3.67 (2H, t, 7.2), 3.08-3.04 (2H, m), 2.57 (5H, bs), 1.84-1.51 (12H, m), 1.49 (9H, s), 1.47 (9H, s), 1.01-0.93 (2H, m).

Step e *N-(Cyclohexanemethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 25 step d replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs), 7.82 (1H, bs), 7.71 (1H, bs), 7.50 (2H, m), 3.56-3.48 (2H, m), 3.29-3.23 (2H, m), 3.16-3.11 (2H, m), 3.00-2.93 (4H, m), 1.98-1.83 (6H, m), 1.71-1.67 (5H, m), 1.47-1.46 (1H, m), 1.21-1.08 (3H, m), 0.95-0.84 (2H). Microanalysis found C 48.04 H 9.69 N 14.98. $C_{15}H_{32}Cl_2N_4$-$2H_2O$ requires C 48.00 H 9.67 N 14.93.

Example 26

N-(Cyclohexanemethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(1-pent-4-enyl)-guanidine.* The title compound was prepared as in Example 14 step b with cyclohexylmethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 9.50 (1H,

bs), 5.85-5.74 (1H, m), 5.06-4.96 (2H, m), 3.66 (2H, t, 7.5), 3.08 (2H, m), 2.08-2.05 (2H, m), 1.79-1.47 (25H, m), 1.29-1.22 (4H, m), 0.97 (2H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(1-butan-4-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 26 step a replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, s), 9.79 (1H, s), 3.69 (2H, t, 6.2), 3.06 (2H, t, 5.7), 2.52-2.47 (2H, m), 1.95-1.85 (2H, m), 1.78-1.69 (5H, m), 1.50 (9H, s), 1.48 (9H, s), 1.28-1.15 (2H, m), 1.02-0.95 (2H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 26 step b replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 3.73-3.64 (2H, m), 3.07 (2H, bt, 6), 2.48 (2H, bs), 1.78-1.47 (32H, m), 1.29-1.14 (3H, m), 1.01-0.90 (2H, m).

Step d *N-(Cyclohexanemethyl)-N'(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product of Example 26 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6)11.0 (1H, bs), 7.90 (1H, bs), 7.80 (1H, bs), 7.51 (2H, m), 3.50-3.45 (2H, m), 3.20-3.07 (4H, m), 3.00-2.96 (4H, m), 1.97-1.85 (4H, m), 1.72-1.45 (10H, m), 1.20-1.08 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 48.40 H 9.90 N 13.96. $C_{16}H_{34}Cl_2N_4$-2.5H_2O requires C 48.23 H 9.87 N 14.06.

Example 27

N-(Cyclohexanemethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(1-hex-5-enyl)-guanidine.* The title compound was prepared as in Example 15 step b with cyclohexylmethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, bs), 5.85-5.75 (1H, m), 5.04-4.94 (2H, m), 3.69-3.64 (2H, m), 3.06 (2H, t, 6), 2.08-2.05 (2H, m), 1.78-1.39 (31H, m), 1.29-1.22 (2H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(1-pentan-5-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 27 step a replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 10-9.50 (1H, s), 9.77 (1H, t, 1.5), 3.69-3.65 (2H, m), 3.05 (2H, d, 6.6), 2.50-2.46 (2H, m), 1.74-1.47 (28H, m), 1.29-1.19 (3H, m), 0.97-0.94 (2H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(cyclohexanemethyl)-N''-(5-pyrrolidin-1-yl-pentyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 27 step b replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, bs), 3.67-3.61 (2H, m), 3.08-3.04 (2H, m), 2.48-2.39 (6H, bs), 1.78-1.47 (31H, m), 1.34-1.21 (6H, m), 0.97 (2H, m).

Step d *N-(Cyclohexanemethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 27 step c replacing the product of Example 2 step b. ^{1}H NMR ($DMSO-d_6$) 10.9 (1H, bs), 7.78 (1H, bs), 7.72 (1H, bs), 7.45 (2H, m), 3.50-3.44 (2H, m), 3.17-2.90 (8H, m), 1.99-1.83 (4H, m), 1.70-1.63 (7H, m), 1.51-1.31 (5H, m), 1.20-1.06 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 55.57 H 9.88 N 15.25. $C_{17}H_{36}Cl_2N_4$ requires C 55.28 H 10.03 N 14.97.

Example 28

N-(1-Adamantanemethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(1-but-3-enyl)-guanidine.* The title compound was prepared as in Example 25 step a with adamantanemethylamine replacing cyclohexylmethylamine. ^{1}H NMR ($CDCl_3$) 10.0 (1H, bs), 5.83-5.72 (1H, m), 5.13-5.03 (2H, m), 3.74 (2H, t, 7.5), 2.89 (2H, s), 2.38-2.30 (2H, m), 2.05-2.02 (3H, bs), 1.77-1.42 (30H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(1-propan-3-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 28 step a replacing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 10.0 (1H, s), 9.79 (1H, bs), 3.97 (2H, bt, 6.6), 2.84-2.78 (4H, m), 2.04-2.02 (3H, bs), 1.77-1.47 (30H, m).

Step c *N-(1-Adamantanemethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* To an ice cooled suspension of N,N'-bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(1-propan-3-al)-guanidine (493mg, 1.06mmol) and pyrrolidine (0.097ml, 1.16mmol) in 1,2-dichloroethane (5ml) was added in a single portion sodium triacetoxyborohydride (394mg, 1.86mmol). The coolant was removed and the resultant suspension stirred at ambient temperature. After 1.5h further pyrrolidine (0.045ml, 0.54mmol) was added and the reaction was stirred at ambient temperature for 1h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (15ml) and extracted twice with ethyl acetate (15ml). The

combined organics were dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (120:10:1 DCM:methanol:ammonia) to give the title compound as an oil. The residue was dissolved in chloroform (5ml) and treated with hydrogen chloride-dioxan (5ml) and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue evaporated twice from dichloromethane (10ml) to give the title compound as a foam (302mg, 73%). ^{1}H NMR (DMSO-d_6) 10.9 (1H, bs), 7.94 (1H, bs), 7.65 (1H, bs), 7.57 (2H, m), 3.53-3.48 (2H, m), 3.29-3.24 (2H, m), 3.17-3.12 (2H, m), 2.99-2.93 (2H, m), 2.83 (2H, d, 5.7), 1.98-1.87 (9H, m), 1.69-1.56 (6H, m), 1.49 (6H, bs). Microanalysis found C 52.99 H 9.57 N 12.92. $C_{19}H_{36}Cl_2N_4$-$2H_2O$ requires C 53.39 H 9.43 N 13.11.

Example 29

N-(1-Adamantanemethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride

Step a *N,N'-Bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(1-pent-4-enyl)-guanidine.* The title compound was prepared as in Example 14 step b with adamantanemethylamine replacing 4-chlorobenzylamine. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, bs), 5.86-5.77 (1H, m), 5.07-4.96 (2H, m), 3.67 (2H, t, 7.5), 2.88 (2H, d, 4.5), 2.09-2.02 (5H, m), 1.73-1.64 (8H, m), 1.56-1.47 (24H, m).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(1-butan-4-al)-guanidine.* The title compound was prepared as in Example 14 step c with the product from Example 29 step a repalcing the product of Example 14 step b. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, s), 9.79 (1H, t, 1.2), 3.72-3.67 (2H, m), 2.87 (2H, bs), 2.51-2.48 (2H, m), 2.05-1.89 (5H, m), 1.73-1.68 (6H, m), 1.54-1.48 (24H, m).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(1-adamantanemethyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine.* The title compound was prepared as in Example 14 step d with the product from Example 29 step b replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 10.0-9.50 (1H, bs), 3.67 (2H, d, 6.9), 2.88 (2H, bt, 5.4), 2.49-2.45 (6H, bm), 2.02 (3H, bs), 1.77-1.53 (20H, m), 1.51 (9H, s), 1.47 (9H, s).

Step d *N-(1-Adamantanemethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 29 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 10.86 (1H, bs), 7.92 (1H, bs), 7.67 (1H, bs), 7.52 (2H, bs), 3.51-3.46 (2H, m), 3.20-3.06 (4H, m), 3.00-2.91 (2H, m), 2.83 (2H, d, 5.7), 2.00-1.84 (7H, m), 1.77-

1.50 (16H, m). Microanalysis found C 54.25 H 9.72 N 12.46. $C_{20}H_{38}Cl_2N_4$-$2H_2O$ requires C 54.41 H 9.59 N 12.69.

Example 30

N-(2-(4-Bromophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(2-(4-bromophenyl)ethyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-bromophenethyl alcohol replacing 4-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) 7.40 (2H, d, 8.4), 7.10 (2H, d, 8.4), 3.73-3.67 (2H, m), 2.97-2.91 (2H, m), 2.38 (3H, s), 1.52 (9H, s), 1.49 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(2-(4-bromophenyl)ethyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 30 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR ($CDCl_3$) 10.0-9.00 (1H, bs), 7.39 (2H, d, 8.4), 7.08 (2H, d, 8.4), 3.87 (2H, t, 7.5), 3.17 (2H, bs), 2.87 (2H, t, 6.9), 2.53 (6H, m), 1.81-1.71 (6H, m), 1.50 (9H, s), 1.46 (9H, s).

Step c *N-(2-(4-Bromophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine dihydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 30 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.12 (1H, bs), 8.00 (1H, bs), 7.89 (1H, bs), 7.64 (2H, bs), 7.47 (2H, d, 9), 7.25 (2H, d, 9), 3.48-3.26 (6H, m), 3.15-3.10 (2H, m), 2.99-2.95 (2H, m), 2.77 (2H, t, 7.2), 1.97-1.87 (6H, m). Microanalysis found C 44.77 H 6.59 N 13.29. $C_{16}H_{27}BrCl_2N_4$ requires C 45.09 H 6.39 N 13.14.

Example 31

N-(4-Chlorobenzyl)-N'-(2-(1-methyl-pyrrolidin-2-yl)-ethyl]-guanidine dihydrochloride. A solution of 1,3'-bis(*tert*-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea (920mg, 2.00mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (0.724ml, 5.00mmol) in THF (20ml) and water (2ml) heated at reflux for 2h. The reaction was partitioned between ethyl acetate (40ml) and water (60ml) and the aqueous phase was discarded. The organic phase was washed with brine (50ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia). The purified residue was dissolved in ethanol (10ml) and

treated with aqueous hydrochloric acid (1M, 10ml) and the reaction heated at reflux for 4h. The solvent was evaporated at reduced pressure and the residue evaporated twice form ethanol (20ml) and chloroform (20ml) to afford the title compound (800mg, 97%). ^{1}H NMR (DMSO-d_6) 10.84 (1H, bs), 8.28 (1H, bs), 8.05 (1H, bt, 6), 7.69 (2H, bs), 7.46-7.23 (4H, m), 4.42 (2H, d, 6), 3.46-2.90 (5H, m), 2.74-2.73 (3H, bs), 2.14-1.87 (6H, m). Microanalysis found C 49.05 H 6.88 N 15.32 $C_{15}H_{25}Cl_3N_4$ requires C 48.99 H 6.85 N 15.24.

Example 32

N-(4-Chlorobenzyl)-N'-(3-morpholin-4-yl-propyl)guanidine dihydrochloride salt. A solution of 1,3'-bis(tert-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea (535mg, 1.29mmol) and 4-(3-aminopropyl)morpholine (0.425ml, 2.91mmol) in THF (10ml) and water (1ml) heated at reflux for 1h. The reaction was partitioned between ethyl acetate (40ml) and water (40ml) and the aqueous discarded. The organic phase was washed with brine (50ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (120:10:1 DCM:methanol:ammonia). The residue was dissolved in chloroform (5ml) and treated with hydrogen chloride-dioxan (5ml) and the solution stirred at ambient temperature for 18h. The solvent was removed at reduced pressure and the residue suspended in dioxan (10ml) and filtration afforded the title compound (120mg, 24%). ^{1}H NMR (DMSO-d_6) 11.20 (1H, s), 8.28 (1H, s), 8.05 (1H, bs), 7.70 (2H, bs), 7.43 (2H, d, 8.4), 7.34 (2H, d, 8.4), 4.42 (2H, d), 4.00-3.79 (4H, m), 3.39-3.35 (6H, m), 3.11-2.99 (2H, m), 1.98-1.91 (2H, m). Microanalysis found C 47.06 H 6.63 N 13.39 $C_{15}H_{25}Cl_3N_4O$-0.28dioxan requires C 47.41 H 6.72 N 13.71.

Example 33

N-(2-Pyrrolidin-1-yl-ethyl)-2-naphthalenesulfonamide

To an ice-cooled solution of N-(2-aminoethyl)pyrrolidine (1.00g, 8.76mmol) and triethylamine (1.221ml, 8.76mmol) in DCM (20ml) was added portionwise 2-naphthalenesulfonyl chloride (1.98g, 8.73mmol). The coolant was removed and the resultant solution stirred at ambient temperature for 16h. The organic phase was washed sequentially twice with water (20ml) and brine (20ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to

obtain the title compound as a white solid (1.81g, 68%). ^{1}H NMR ($CDCl_3$) 8.45 (1H, d, 1.5), 7.99-7.83 (4H, m), 7.66-7.61 (2H, m), 3.06-3.02 (2H, m), 2.53 (2H, m), 12.36-2.32 (4H, m), 1.74-1.65 (4H, m). Microanalysis found C 62.96 H 6.74 N 9.11. $C_{16}H_{20}N_2O_2S$ requires C 63.13 H 6.62 N 9.20.

Example 34

N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfonamide

Step a *N-(3-Hydroxy-propyl)-2-naphthalenesulfonamide*. To an ice-cooled solution of 3-amino-1-propanol (1.69ml, 22.09mmol) and triethylamine (3.69ml, 26.5mmol) in DCM (25ml) was added a solution of 2-naphthalenesulfonyl chloride (5.00g, 22.06mmol) in DCM (25ml). The coolant was removed and the solution stirred at ambient temperature for 16h. The organic solution was washed sequentially with water (50ml), aqueous citric acid (10%, 50ml) and brine (50ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (silica 2:1 ethyl acetate:hexane) to obtain the the title compound as a white solid (3.56g, 61%). ^{1}H NMR ($CDCl_3$) 8.45 (1H, d, 1.2), 7.99-7.83 (4H, m), 7.66-7.61 (2H, m), 5.27 (1H, t, 6), 3.74 (2H, t, 5.4), 3.17 (2H, q, 6), 1.91 (1H, bs), 1.76-1.68 (2H, m).

Step b *N-(3-Chloro-propyl)-2-naphthalenesulfonamide*. A solution of N-(3-hydroxy-propyl)-2-naphthalenesulfonamide (3.56g, 13.4mmol) and triphenylphosphine (5.28g, 20.1mmol) in carbon tetrachloride (50ml) and chloroform (50ml) were heated at reflux for 74h. Further triphenylphosphine (1.00g, 3.81mmol) was added and the reaction mixture was heated at reflux for a further 4h. The solvent was removed at reduced pressure and the residue purified by flash column chromatography (2:1 hexane:ethyl acetate) to obtain the title compound (2.187g, 58%). ^{1}H NMR ($CDCl_3$) 8.46 (1H, d, 1.5), 8.00-7.83 (4H, m), 7.68-7.63 (2H, m), 4.68 (1H, t, 6.3), 3.56 (2H, t, 6.3), 3.16 (2H, q, 6.6), 2.05 -1.93 (2H, m).

Step c *N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfonamide.* A solution of N-(3-chloro-propyl)-2-naphthalenesulfonamide (500mg, 1.76mmol) and pyrrolidine (0.736ml, 8.82mmol) in DCM (5ml) was stirred at ambient temperature for 30h. The solution was diluted with further DCM (20ml) and washed sequentially twice with water (20ml) and brine (20ml), and the organic phase dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (silica, 90:10:1 DCM:methanol:ammonia).

The residue was triturated with ether (50ml) to obtain the title compound as a white solid (50mg, 9%). ^{1}H NMR ($CDCl_3$) 8.43 (1H, s), 7.99-7.59 (7H, m), 3.11 (2H, t, 5.7), 2.54-2.49 (6H, m), 1.81 (4H, m), 1.68-1.63 (2H, m). Microanalysis found C 63.85 H 7.04 N 8.76. $C_{17}H_{22}N_2O_2S$ requires C 64.12 H 6.96 N 8.80.

Example 35

N-(4-Pyrrolidin-1-yl-butyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 33 with N-(4-aminobutyl)pyrrolidine[1] replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.41(1H, s), 7.90 (4H,m), 7.60 (2H,m), 2.96 (2H, t), 2.69 (4H, m), 2.59(2H, t), 1.92 (4H, m), 1.61 (4H, m). The hydrochloride salt was prepared in hydrogen chloride-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.49, H 6.90, N 7.14. $C_{18}H_{25}ClN_2O_2S$ requires C 57.26, H 6.93, N 7.42.

Example 36

N-(2-Piperidin-1-yl-ethyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 33 with 1-(2-aminoethyl)piperidine replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.45 (1H, s), 7.93 (3H,m), 7.83 (1H, m), 7.64 (2H,m), 2.99 (2H, t), 2.31 (2H, t), 2.14 (4H, m), 1.44 (6H, m). Found C 63.88, H 7.03, N 8.87. $C_{17}H_{22}N_2O_2S$ requires C 64.12, H 6.96, N 8.79.

Example 37

N-(4-(4-Methyl-piperazin-1-yl)-butyl)-2-naphthalenesulfonamide

Step a *N-(4-(4-Methyl-piperazin-1-yl)-butyl)-phthalimide.* To a solution of 1-methylpiperazine (2.8ml, 25.0mmol) in acetonitrile (20ml) was added the solution of N-(4-bromobutyl)phthalimide (2.82g, 10.0mmol) in acetonitrile (20ml). The mixture was stirred at ambient temperature overnight, the solvent was evaporated and the residue was dissolved in DCM (30 ml). The solution was washed with water (2x30 ml), dried over anhydrous magnesium sulfate, then concentrated. The crude product was purified by flash column chromatography (silica; DCM:methanol 85:15) to afford the product as a foam (1.64 g, 54%). ^{1}H NMR ($CDCl_3$) 7.83 (2H, m), 7.70 (2H, m), 3.70 (2H, t), 2.44-2.33(10H, m), 2.26 (3H, s), 1.69 (2H, m), 1.54 (2H, m).

Step b *4-(4-Methyl-piperazin-1-yl)-butylamine.* To a solution of N-(4-(4-methyl-piperazin-1-yl)-butyl)-phthalimide (1.6 g, 5.3 mmol) in ethanol (30 ml) was added hydrazine hydrate (1.4 ml, 26.5 mmol) and the mixture was stirred under reflux for 2h

then allowed to cool to ambient temperature. The precipitate was filtered and the filtrate was evaporated. The residue was suspended in chloroform, the precipitate was filtered and the filtrate was evaporated to afford the product as a yellow oil (1.0 g). ^{1}H NMR (DMSO-d_6) 3.30 (4H, br, s), 2.53 (2H, m), 2.22(8H, m), 2.12 (3H, s), 1.37 (4H, m).

Step c *N-(4-(4-Methyl-piperazin-1-yl)-butyl)-2-naphthalenesulfonamide.* The title compound was prepared as in Example 33 with the product from Example 37 step b replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.43(1H, s), 7.86 (4H,m), 7.63 (2H,m), 3.00 (2H, t), 2.54 (8H, m), 2.32 (6H, m), 1.54 (4H, m). The dihydrochloride salt was prepared with hydrogen chloride-dioxan, the solvent was evaporated to afford the title compound as a white solid. Found C 52.14, H 6.92, N 9.58. $C_{19}H_{29}Cl_2N_3O_2S$ requires C 52.53, H 6.73, N 9.67.

Example 38

N-(2-Pyrrolidin-1-yl-ethyl)-N-methyl-2-naphthalenesulfonamide.

To an ice-cooled solution of 2-naphthalenesulfonyl chloride (2.27g, 10.0mmol) and triethylamine (2.00ml, 14.4mmol) in DCM (30ml) was added methyl-(2-pyrrolidin-1-yl-ethyl)-amine[2] (1.28g, 10.0mmol). The coolant was removed and the resultant solution stirred at ambient temperature for 1.5h. The organic phase was washed sequentially twice with water (30ml), then brine (30ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (100:10:1 DCM:methanol:ammonia). The purified material was treated with aqueous hydrochloric acid (1M, 20ml) and the resultant solid was removed by filtration and dried *in vacuo* to obtain the title compound as a white solid (909mg, 26%). ^{1}H NMR (DMSO-d_6) 10.52 (1H, bs), 8.51 (1H, s), 8.22-8.07 (3H, m), 7.84-7.68 (3H, m), 3.59-3.37 (6H, m), 3.09-3.01 (2H, m), 2.77 (3H, s), 2.01-1.87 (4H, m). Microanalysis found C 57.28 H 6.74 N 7.83. $C_{17}H_{23}ClN_2O_2S$ requires C 57.53 H 6.53 N 7.89.

Example 39

N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide.

Step a *Naphthalene-2-sulfinic acid methyl ester.* To a ice-cooled suspension of 2-naphthalenethiol (2.16g, 18.7mmol) and potassium carbonate (5.68g, 41.1mmol) in methanol (60ml) was added N-bromosuccinimide (7.32g, 41.1mmol). The coolant

was removed after 10 minutes and the reaction mixture stirred at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (70ml) and washed sequentially with water (100ml), twice with saturated aqueous sodium hydrogen carbonate (70ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound as a white solid (2.335g, 83%). ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 8.01-7.92 (3H, m), 7.72-7.60 (3H, m), 3.51 (3H, s).

Step b *N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide.* To a cooled (-30^{0}C) solution of N-(3-aminopropyl)pyrrolidine (641mg, 5.00mmol) in THF (10ml) was added a solution of lithium diisopropylamide (1.5M, 3.30ml, 4.95mmol). The solution was stirred at this temperature for 20 minutes and then added dropwise to a cooled (-78^{0}C) solution of naphthalene-2-sulfinic acid methyl ester (1.03g, 5.00mmol) in THF (10ml). The reaction was stirred at this temperature for 3h and then allowed to warm to ambient temperature and stirred at ambient temperature for 16h. The reaction was quenched with saturated aqueous ammonium chloride (70ml) and then extracted thrice with ethyl acetate (70ml). The combined organics were extracted with aqueous hydrochloric acid (1M, 100ml) and the acidic phase washed with ethyl acetate (70ml). The pH of the acidic phase was adjusted (pH11) with ammonia (880) and extracted thrice with DCM (70ml). The combined DCM extracts were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography to obtain the title compound (54mg, 3%). The title compound was converted to the corresponding hydrochloride salt with hydrogen chloride-dioxan. ^{1}H NMR (DMSO-d_6) 9.79 (1H, s), 8.43-8.06 (4H, m), 7.83-7.67 (4H, m), 3.45-3.44 (2H, m), 3.10-3.07 (2H, m), 2.90-2.81 (4H, m), 1.95-1.74 (6H, m). Microanalysis found C 57.43 H 6.75 N 7.73. $C_{17}H_{23}ClN_2OS$-0.5HCl requires C 57.17 H 6.63 N 7.84.

Example 40

4-(Pyrrolidin-1-yl-butyl)-2-naphthalenesulphone

Step a *4-(2-Naphthalenesulfanyl)-butanoic acid ethyl ester.* To a stirred ice-cooled solution of 2-naphthalenethiol (3.20g, 20.0mmol) in DMF (40ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 880mg, 22.0mmol). The suspension was stirred at this temperature for 15 minutes and then treated with a

solution of ethyl 4-bromobutyrate (3.15ml, 22.0mmol) in DMF (20ml). The coolant was removed and the reaction stirred at ambient temperature for 16h. The reaction was partitioned between ethyl acetate (200ml) and water (200ml), and the aqueous phase discarded. The organic phase washed twice with brine (200ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (5:1 hexane:ethyl acetate) to afford the title compound (4.56%, 83%). ^{1}H NMR ($CDCl_3$) 7.78-7.74 (4H, m), 7.48-7.42 (3H, m), 4.15 (2H, q, 7.2), 3.08 (2H, t, 7.2), 2.50 (2H, t, 7.2), 2.07-1.97 (2H, m), 1.25 (3H, t, 7.2).

Step b *4-(2-Naphthalenesulfonyl)-butyric acid ethyl ester.* To a solution of 4-(2-naphthalenesulfanyl)-butanoic acid ethyl ester (1.04g, 3.80mmol) in DCM (10ml) was added in a single portion *meta*-chloroperoxybenzoic acid (3.27g, 11.37mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The reaction diluted with DCM (70ml) and washed sequentially with saturated aqueous sodium hydrogen carbonate (100ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound (1.02g, 88%). ^{1}H NMR ($CDCl_3$) 8.50 (1H, s), 8.04-7.86 (4H, m), 7.70-7.42 (2H, m), 4.09 (2H, q, 7.2), 3.30-3.25 (2H, m), 2.46 (2H, t, 7.2), 2.12-2.05 (2H, m), 1.22 (3H, t, 7.2).

Step c *4-(2-Naphthalenesulfonyl)-butan-1-ol.* To a cooled (-78^{0}C) solution of 4-(2-naphthalenesulfonyl)-butyric acid ethyl ester (1.00g, 3.27mmol) in THF (10ml) was added dropwise a solution of lithium aluminium hydride (1M, THF, 3.50ml, 3.50mmol) and the reaction stirred at this temperature for 3h. The reaction was treated sequentially with water (0.14ml), aqueous sodium hydroxide (2M, 0.14ml) and water (0.42ml) and allowed to warm to ambient temperature. Sodium sulfate was added and the resultant suspension filtered through a pad of celite and the filtercake washed with further ethyl acetate (150ml). The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to afford the title compound (524mg, 61%). ^{1}H NMR ($CDCl_3$) 8.50 (1H, s), 8.04-7.86 (4H, m), 7.72-7.63 (2H, m), 3.66-3.62 (2H, m), 3.27-3.21 (2H, m), 1.91-1.83 (2H, m), 1.71-1.65 (2H, m), 1.56 (1H, bs).

Step d *4-(2-Naphthalenesulfonyl)-butyraldehyde.* To a solution of 4-(2-naphthalenesulfonyl)-butan-1-ol (524mg, 1.98mmol) and triethylamine (0.829ml,

5.96mmol) in DMSO (10ml) was added a solution of sulfur trioxide-pyridine (948mg, 5.96mmol) in DMSO (10ml) and the reaction mixture stirred at ambient temperature for 15 minutes. The reaction was poured into ice-water (150ml) and then extracted thrice with ethyl acetate (60ml). The combined organic phases were washed with aqueous citric acid (70ml) and brine (70ml), then dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (2:1 ethyl acetate:hexane) to afford the title compound (457mg, 88%). ^{1}H NMR ($CDCl_3$) 9.75 (1H, s), 8.50 (1H, s), 8.05-7.65 (6H, m), 3.26-3.22 (2H, m), 2.71 (2H, t, 6.9), 2.15-2.04 (2H, m).

Step e *4-(Pyrrolidin-1-yl-butyl)-2-naphthalenesulphone.* The title compound was prepared as in Example 14 step d with the product from Example 40 replacing the product of Example 14 step c. ^{1}H NMR ($CDCl_3$) 8.50 (1H, m), 8.04-7.86 (4H, m), 7.72-7.64 (2H, m), 3.24-3.19 (2H, m), 2.42-2.37 (6H, m), 1.86-1.56 (8H, m). Microanalysis found C 68.22 H 7.45 N 4.38. $C_{18}H_{23}NO_2S$ requires C 68.10 H 7.30 N 4.41.

Example 41

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 33 with 2-(2-aminoethyl)-1-methylpyrrolidine replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.42 (1H, s), 7.85 (4H,m), 7.62 (2H,m), 3.05 (3H, m), 2.26 (1H, m), 2.25(3H, s), 2.10 (1H, m), 1.76-1.48 (6H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.21, H 6.79, N 7.96. $C_{17}H_{23}Cl\ N_2O_2S$ requires C 57.53, H 6.53, N 7.89.

Example 42

N-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide

Step a *N-(tert-Butoxycarbonyl)-2-piperidin-2-yl-ethanol.* To a stirred solution of 2-(2-hydroxyethyl)piperidine (24.22g, 187mmol) in dioxan (450ml) was added dropwise a solution of di-*tert*-butyldicarbonate (40.9g, 187mmol) in dioxan (50ml) and the resultant solution was stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue partitioned between ethyl acetate (200ml) and aqueous citric acid (10%, 200ml). The aqueous was discarded and the organic washed sequentially with saturated aqueous sodium hydrogen carbonate (200ml) and

brine (200ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to give the title compound as an oil (100%). ^{1}H NMR ($CDCl_3$) 4.40 (1H, bm), 3.97-3.93 (1H, bm), 3.63-3.56 (1H, bm), 3.36 (1H, bm), 2.72-2.63 (1H, m), 1.98-1.89 (1H, m), 1.75-1.27 (16H, m).

Step b *2-(2-Amino-ethyl)-piperidine-1-carboxylic acid t-butyl ester*. To an ice-cooled solution of N-(*tert*-butoxycarbonyl)-2-piperidin-2-yl-ethanol (5.00g, 21.8mmol) , triphenylphosphine (7.41g, 28.3mmol) and phthalimide (4.16g, 28.3mmol) in THF (50ml) was added dropwise diethylazodicarboxylate (4.45ml, 28.3mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). A solution of this material in ethanol (100ml) was treated with hydrazine hydrate (5.30ml) and the resultant reaction mixture was heated at reflux for 1h. The resultant solid was removed by filtration and the filter-cake washed with further ethanol (50ml). The filtrate was evaporated at reduced pressure and the residue was suspended in chloroform (50ml) and the solid residue was removed by filtration. The filtrate was evaporated at reduced pressure to afford the title compound as an oil (2.58g, 52%). ^{1}H NMR ($CDCl_3$) 4.36 (1H, bs), 3.95 (1H, bd, 13.5), 2.77-2.60 (3H, m), 1.99-1.93 (1H, m), 1.70-1.38 (18H, m).

Step c *N-(2-(1-(tert-butoxycarbonyl) piperidin-2-yl)-ethyl)-naphthalenesulfonamide.* The title compound was prepared as in Example 33 with the product from Example 42 step b replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.42 (1H, m), 7.97-7.82 (4H, m), 7.64-7.59 (2H, m), 4.28-4.24 (1H, m), 3.88-3.84 (1H, m), 3.19 (1H, m), 2.60-2.53 (2H, m), 1.91-1.87 (1H, m), 1.64-1.28 (16H, m).

Step d *N-(2-(Piperidin-2-yl)-ethyl)-naphthalenesulfonamide.* To a solution of N-(2-(1-(*tert*-butoxycarbonyl) piperidin-2-yl)-ethyl)-naphthalenesulfonamide (3.29g, 7.89mmol) in $CHCl_3$ (8ml) was added trifluoroacetic acid (16ml) and the reaction mixture was stirred at ambient temperature for 20h. The excess trifluoroacetic acid was removed at reduced pressure and the residue partitioned between aqueous potassium carbonate (10%, 50ml) and $CHCl_3$ (50ml). The $CHCl_3$ layer was removed and the organic phase extracted with further $CHCl_3$ (50ml). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound (2.42g, 97%). ^{1}H NMR ($CHCl_3$) 8.43 (1H, d, 1.5), 7.98-7.86 (4H, m), 7.76-7.60 (2H, m), 3.20-3.01 (5H, m), 2.60-2.55 (2H, m), 1.60-1.19 (8H, m).

Step e *N-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide.* To a stirred solution of N-(2-(piperidin-2-yl)-ethyl)-naphthalenesulfonamide (2.42g, 7.63mmol) and aqueous formaldehyde (37%, 3.3ml) in acetonitrile (25ml) was added portionwise sodium cyanoborohydride (788mg, 11.4mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The pH was adjusted to 6 with acetic acid and the resultant solution stirred at ambient temperature for 30 minutes. The mixture was evaporated at reduced pressure and the residue treated with methanol (50ml) and ammonia solution (880, 50ml). The aqueous phase was extracted twice with DCM (50ml) and the combined organics dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (338mg, 13%) as an oil. The oil was treated with hydrogen chloride-dioxan and the solvent removed *in vacuo*. The residue was suspended in diethyl ether and the solid removed by filtration, to obtain the title compound as the hydrochloride salt. ^{1}H NMR (DMSO-d_6) 10.46-10.23 (1H, bs), 8.45-7.64 (8H, m), 3.01 (1H, m), 3.03-2.80 (4H, m), 2.64-2.56 (3H, m), 2.06-1.34 (8H, m). Microanalysis found C 57.43 H 7.08 N 7.27. $C_{18}H_{25}ClN_2O_2S$-0.5H_2O requires C 57.21 H 6.93 N 7.41.

Example 43

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide

Step a *2S-(Methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.* To a solution of N-tert-Butoxycarbonyl-L-proline (10.76 g, 50 mmol), N,N-diisopropylethylamine (9.6 ml, 55 mmol), N,O-dimethylhydroxylamine hydrochloride (5.36 g, 55 mmol) and 1-hydroxybenzotriazole (6.75g, 50 mmol) in DCM (150 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.5 g, 50 mmol) at 0°C. The solution was stirred at ambient temperature for 16h, washed with water (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), 1N hydrochloric acid (100 ml), and water again (100 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to afford the product as a colourless oil (11.1 g, 86%). ^{1}H NMR ($CDCl_3$) 4.70 and 4.60 (1H, 2xm), 3.76 and 3.69 (3H, 2xs), 3.60-3.30 (2H, m), 2.10-1.75 (4H, m), 1.43 and 1.39 (9H, 2xs).

Step b *2S-Formyl-pyrrolidine-1-carboxylic acid tert-butyl ester.* To a suspension of lithium aluminium hydride (2.12 g, 56.0 mmol) in THF (80 ml) was added dropwise a

solution of 2S-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11.1 g, 43 mmol) in THF (80 ml) at 0°C under argon. The temperature was allowed to rise to ambient temperature and the stirring was continued for 1h. The reaction mixture was cooled to 0°C and 2N sodium hydroxide solution (11 ml) was slowly added. The mixture was stirred at ambient temperature for 30 mins, the precipitate was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in ethyl acetate (50 ml) and the solution was successively washed with 1 N hydrochloric acid (30 ml), water (30 ml) and brine (30 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated to afford the product as a colourless oil (6.3 g, 74%). ^{1}N NMR ($CDCl_3$) 9.51 and 9.42 (1H, 2xs), 4.10 and 4.00 (1H, 2xm), 3.45 (2H, m), 1.93 (4H, m), 1.43 and 1.40 (9H, 2xs).

Step c *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-acrylic acid ethyl ester.* 2S-Formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (6.3 g, 31.6 mmol) and (carbethoxymethylene)triphenylphosphorane (11.0 g, 31.6 mmol) were refluxed in THF (50 ml) for 2h. The solvent was evaporated and the residue was triturated with hexane:ethyl acetate 1:1 (60 ml). The precipitate was filtered, the filtrate was evaporated. The residue was purified by flash column chromatography (silica; hexane:ethyl acetate 80:20) to afford colourless oil (8.2 g, 97%). %). ^{1}N NMR ($CDCl_3$) 6.80 (1H, bd), 5.80 (1H, d), 4.50 and 4.55 (1H, 2xbs), 4.15 (2H, m), 3.41 (2H, m), 2.00 (1H, m), 1.77 (3H, m), 1.40 (9H, s), 1.24 (3H, t).

Step d *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propionic acid ethyl ester* A round bottom flask containing 3-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-acrylic acid ethyl ester (8.1 g, 30.2 mmol), 10% palladium-on-charcoal (0.80 g) and THF:methanol 1:1 (150 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred for 2h under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated the title compound as a colourless oil (7.3g, 89%). ^{1}N NMR ($CDCl_3$) 4.10 (2H, m), 3.79 (1H,bs), 3.29 (2H, m), 2.29 (2H, m), 1.90-1.61 (6H, m), 1.43 (9H, s), 1.23 (3H, t).

Step e *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 40 step c with the product from Example 43 step d replacing the product of Example 40 step b. ^{1}H NMR (DMSO-d_6) 4.34 (1H, t), 3.62 (1H, m), 3.38 (2H, m), 3.22 (2H, m), 1.85-1.23 (17H, m).

Step f *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propylamine*. The title compound was prepared as in Example 42 step b with the product from Example 43 step e

replacing the product of Example 42 step a. ^{1}H NMR (DMSO-d_6) 3.61 (1H, bs), 3.36 (2H, bs), 3.20 (2H, m), 2.49 (2H, m), 1.82-1.16 (17H, m).

Step g *N-(3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide* The title compound was prepared as in Example 33 with the product from Example 43 step f replacing N-(2-aminoethyl)pyrrolidine. ^{1}H NMR ($CDCl_3$) 8.44 (1H, s), 7.92 (4H, m), 7.60 (2H, m), 5.70 and 4.50 (1H, 2xbs), 3.72 (1H, bs), 3.25 (2H, m), 3.04 (2H, m), 1.87- 1.24 (17H, m).

Step h *N-(3-(Pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide* The title compound was prepared as in Example 42 step d with the product from Example 43 step g replacing the product of Example 42 step c. ^{1}H NMR (DMSO-d_6) 8.41(1H, s), 8.11 (2H, m), 8.03 (1H, d), 7.80 (1H, m), 7.67 (2H, m), 6.00 (1H, bs), 2.92-2.75 (5H, m), 1.75 (1H, m), 1.60 (2H, m), 1.39 (4H, m), 1.15 (1H, m).

Step i *N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide.* The title compound was prepared as in Example 42 step e with the product from Example 43 step h replacing the product of Example 42 step d. ^{1}H NMR ($CDCl_3$) 8.42 (1H, s), 7.86 (4H, m), 7.63 (4H, m), 3.20 (1H, m), 3.06 (1H, m), 2.83 (1H, m), 2.30 (5H, m), 1.83-1.53 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 55.59, H 7.06, N 7.23. $C_{18}H_{25}$ Cl N_2O_2S-1.1 mol of H_2O requires C 55.61, H 7.05, N 7.21.

Example 44

N-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide.

Step a *N-(3-Pyridin-3-yl-propyl)phthalimide.* To a stirred ice-cooled solution of 3-pyridinepropanol (1.29ml, 10.0mmol), triphenylphosphine (3.41g, 13.0mmol) and phthalimide (1.91g, 13.0mmol) in THF (20ml) was added in three portions diethylazodicarboxylate (2.23ml, 13.0mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 20h. The reaction mixture was diluted with ethyl acetate (50ml) and extracted twice with aqueous hydrochloric acid (60ml). The acidic phases were combined and treated with ammonia (880) until pH 11 was achieved and then extracted twice with DCM (100ml). The combined organics were washed with brine (100ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to obtain the title compound (2.67g,

100%). ^{1}H NMR ($CDCl_3$) 8.47-8.41 (2H, m), 7.86-7.46 (5H, m), 7.26-7.20 (1H, m), 3.77 (2H, t, 7.2), 2.70 (2H, t, 7.8), 2.10-2.00 (2H, m).

Step b *N-((1-Methyl-pyridin-3-yl)-propyl)phthalimide iodide.* To a solution of N-(3-pyridin-3-yl-propyl)phthalimide (1.33g, 5.00mol) in acetone (5ml) was added iodomethane (0.467ml, 7.50mmol) and the resultant solution heated at reflux for 4h. The resultant suspension was filtered and the recovered solid washed with ether (50ml) and the title compound (1.50g, 74%) was dried *in vacuo*. ^{1}H NMR (DMSO-d_6) 8.93 (1H, s), 8.82-8.80 (1H, d, 6), 8.48-8.46 (1H, m), 8.06-8.00 (1H, m), 7.89-7.82 (4H, m), 4.29 (3H, s), 3.65 (2H, t, 6.6), 2.84 (2H, t, 8.1), 2.07-1.93 (2H, m).

Step c *N-(3-(1-Methyl-piperidin-3-yl)-propyl)phthalimide* To a cooled (-78^{0}C) suspension of N-((1-methyl-pyridin-3-yl)-propyl)phthalimide iodide (1.49g, 3.65mmol) in methanol (36ml) was added portionwise sodium borohydride (270mg, 7.30mmol) and the resultant suspension stirred at this temperature for 20 minutes. The suspension was allowed to warm to 0^{0}C and the reaction stirred for a further 30 minutes. The suspension was treated with aqueous hydrochloric acid (2M, 3.6ml) and stirring continued for a further 1h. The reaction mixture was treated with sufficient aqueous sodium hydroxide (2M) to pH 11 and water (100ml) added. The aqueous was extracted thrice with DCM (100ml) and the combined organics dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue dissolved in methanol (10ml) and treated with palladium on charcoal (150mg). The resultant suspension was stirred under a hydrogen atmosphere (*via* balloon) for 16h. The suspension was filtered through a pad of celite and the filtercake washed with methanol (100ml). The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (437mg, 42%). ^{1}H NMR ($CDCl_3$) 7.87-7.82 (2H, m), 7.74-7.69 (2H, m), 3.72-3.65 (2H, m), 2.89-2.82 (2H, m), 2.28 (3H, s), 1.89-0.84 (11H, m).

Step d *N-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide*. To a stirred solution of N-(3-(1-methyl-piperidin-3-yl)-propyl)phthalimide (437mg, 1.53mmol) in ethanol (10ml) was added hydrazine hydrate (0.37ml) and the reaction heated at reflux for 1.5h. The resultant suspension was filtered and the filtercake washed with further ethanol (20ml) and the filtrate was evaporated. The residue was suspended in DCM (20ml) and the solid was removed by filtration. The filtrate was evaporated at reduced pressure and the residue dissolved in DCM (5ml). The solution was treated sequentially, with ice-cooling, with triethylamine (0.290ml, 2.08mmol) and 2-

naphthalenesulfonyl chloride (217mg, 1.39mmol). The coolant was removed and the reaction stirred at ambient temperature for 2h. The reaction was diluted with DCM (20ml), washed with water (20ml) and brine (20ml), and dried over dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to afford the title compound (240mg, 45%). ^{1}H NMR ($CDCl_3$) 8.44 (1H, d, 1.2), 7.99-7.59 (6H, m), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.24 (3H, s), 1.87-1.84 (3H, m), 1.64-1.46 (5H, m), 1.21-1.13 (2H, m), 0.75 (1H, m). Microanalysis found C 64.32 H 7.75 N 7.59. $C_{19}H_{26}N_2O_2S$-0.5H_2O requires C 64.19 H 7.76 N 7.88.

Example 45

N-(1-Methyl-piperidin-4-yl)-propyl)-2-naphthalenesulfonamide.

Step a *N-(3-Pyridin-4-yl-propyl)phthalimide.* The title compound was prepared as in Example 44 step a with 4-pyridinepropanol replacing 3-pyridinepropanol. ^{1}H NMR ($CDCl_3$) 8.39 (2H, d, 6), 7.86-7.79 (4H, m), 7.22 (2H, d, 6), 3.60 (2H, t, 6.9), 2.64 (2H, t, 7.2), 1.98-1.88 (2H, m).

Step b *N-((1-Methyl-pyridin-4-yl)-propyl)phthalimide iodide.* The title compound was prepared as in Example 44 step b with the product from Example 45 step a replacing the product of Example 44 step a. ^{1}H NMR (DMSO-d_6) 8.82 (2H, d, 6.6), 7.99 (2H, d, 6.6), 7.89-7.82 (4H, m), 4.24 (3H, s), 3.64 (2H, t, 6.6), 2.93 (2H, t, 7.8), 2.02-1.95 (2H, m).

Step c *N-(3-(1-Methyl-piperidin-4-yl)-propyl)phthalimide* The title compound was prepared as in Example 44 step c with the product from Example 45 step b replacing the product of Example 44 step b. ^{1}H NMR ($CDCl_3$) 7.86-7.71 (4H, m), 3.67 (2H, t, 7.2), 2.88-2.81 (2H, m), 2.25 (3H, s), 1.90-1.30 (11H, m).

Step d *N-(1-Methyl-piperidin-4-yl)-propyl)-2-naphthalenesulfonamide*. The title compound was prepared as in Example 44 step d with the product from Example 45 step c replacing the product of Example 44 step c. ^{1}H NMR ($CDCl_3$) 8.44 (1H, d, 1.8), 7.99-7.82 (4H, m), 7.66-7.62 (2H, m), 4.46 (1H, bm), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.23 (3H, s), 1.85-1.42 (6H, m), 1.21-1.11 (5H, m). Microanalysis found C 66.06 H 7.58 N 8.05. $C_{19}H_{26}N_2O_2S$ requires C 65.86 H 7.56 N 8.09.

Example 46

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-1-naphthalenesulfonamide.

The title compound was prepared as in Example 41 with 1-naphthalenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride. ^{1}H NMR ($CDCl_3$) 8.67 (1H, d), 8.25 (1H, m), 8.06 (1H, d), 7.95 (1H,d), 7.57 (3H,m), 3.07 (1H, m), 2.90 (2H, m), 2.27 (4H, m), 2.00(1H, m), 1.81 (1H, m), 1.55 (4H, m), 1.41 (2H, m). Found C 63.73, H 6.95, N 9.01. $C_{17}H_{22}N_2O_2S$ requires C 64.12, H 6.96, N 8.80.

Example 47

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-toluenesulfonamide.

The title compound was prepared as in Example 41 with 4-toluenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride. The hydrochloride salt was prepared by treatment with hydrogen chloride-dioxan. ^{1}H NMR (DMSO-d_6) 7.62 (2H, d, 8.1), 7.47 (1H, t, 5.1), 7.37 (2H, d, 8.1), 2.86-2.70 (3H, m), 2.37 (3H, s), 2.09 (3H, s), 1.98-1.93 (2H, m), 1.76-1.49 (4H, m)1.29-1.16 (2H, m). Microanalysis found C 52.52 H 7.30 N 8.53. $C_{14}H_{23}ClN_2O_2S$ requires C 52.73 H 7.27 N 8.79.

Example 48

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-chlorophenylsulfonamide.

The title compound was prepared as in Example 41 with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride. The hydrochloride salt was prepared by treatment with hydrogen chloride-dioxan. ^{1}H NMR (DMSO-d_6) 8-7 (1H, bs), 7.82-7.77 (2H, m), 7.50-7.46 (2H, m), 3.10-3.01 (3H, m), 2.39 (1H, m), 2.28 (3H, s), 2.15-2.12 (1H, m), 1.82-1.42 (6H, m). Microanalysis found C 51.65 H 6.44 N 8.99. $C_{13}H_{19}ClN_2O_2S$ requires C 51.56 H 6.32 N 9.25.

Example 49

N-(2-(1-Methyl-pyrrolidin-2S-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide.

Step a *2S-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester.* The title compound was prepared as in Example 42 step a with (S)-(+)-pyrrolidinemethanol replacing 2-(2-hydroxyethyl)piperidine. ^{1}H NMR ($CDCl_3$) 3.94 (1H, m), 3.61 (2H, m), 3.45 (1H, m), 3.30 (1H, m), 2.01 (1H, m), 1.79 (2H, m), 1.58 (1H, m), 1.52 (1H, s), 1.47 (9H, s).

Step b *2S-Tosyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester.* To a solution of 2S-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.0 g, 20.0 mmol) and triethylamine (3.3 ml, 24.0 mmol) in DCM (100 ml) was added p-toluenesulfonyl chloride (3.8 g, 20.0 mmol) and 4-dimethylaminopyridine (0.2 g) at 0°C. The solution was stirred at ambient temperature for 5h, then it was washed successively with water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography (silica; hexane:ethyl acetate 70:30) to afford the title compound (4.3 g, 61 %). ^{1}H NMR ($CDCl_3$) 7.77 (2H, d), 7.34 (2H, d), 4.10 (1H, m), 3.90 (2H, m), 3.29 (2H, m), 2.44 (3H, s), 1.92-1.80 (4H, m), 1.37 (9H, s).

Step c *2S-Cyanomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester.* 2S-Tosyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.3 g, 12.1 mmol) and potassium cyanide (1.6 g, 24.2 mmol) were heated together in dimethyl sulfoxide at 110°C under an atmosphere of argon for 3h. The reaction mixture was cooled to ambient temperature and poured over water (200 ml). The product was extracted with ethyl acetate (3x50 ml), the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica; hexane:ethyl acetate 70:30) to afford the the title compound as a colourless oil (1.46 g, 57.5%). ^{1}H NMR ($CDCl_3$) 4.00 (1H, bs), 3.41 (2H,m), 2.74 (2H, m), 2.16 (1H, m), 1.92 (3H, m), 1.47 (9H, s).

Step d *2S-(2-Amino-ethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.* 2S-Cyanomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.45 g, 6.9 mmol) was suspended in methanol saturated with ammonia (50 ml), Raney-Nickel (*ca.* 1.0 g) and hydrogen hexachloroplatinate(IV)hydrate (80 mg dissolved in 1 ml of water) were added . The mixture was stirred in a Parr bottle under H_2 pressure (about 40 psi) for 24 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude material was purified by flash chromatography (silica; DCM:methanol: amonia (880) 90:10:1) to afford the title amine as a yellow oil (1.18g, 80%). ^{1}H NMR ($CDCl_3$) 3.90 (1H, m), 3.30 (2H, m), 2.71 (2H, t), 1.87-1.45 (17H, m).

Step e *N-(2-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl-ethyl)-(4-chlorophenyl)methanesulfonamide.* To a solution 2S-(2-amino-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.27g, 1.26mmol) and triethylamine (0.23ml,

1.62mmol) in DCM (15 ml), cooled under an atmosphere of argon to -78°C, was added dropwise a solution of (4-chlorophenyl)methanesulfonyl chloride[3] (0.34g, 1.5mmol) in DCM (5 ml). The resultant solution was stirred for 18h, allowing to warm to ambient temperature. The solution was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography (silica; DCM:ethyl acetate 90:10) afforded the product (0.29g, 57%). ^{1}H NMR ($CDCl_3$) 7.34 (4H,s), 6.15 (1H, bs), 4.20 (2H, s), 3.96 (1H, m), 3.28 (2H, m), 3.02 (2H, m), 2.80 (1H, m), 1.95-1.45 (6H, m), 1.45 (9H, s).

Step f *N-(2-(1-Methyl-pyrrolidin-2S-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide.* N-(2-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl-ethyl)-(4-chlorophenyl)methanesulfonamide (0.29 g, 0.72 mmol) was dissolved in trifluoroacetic acid (3 ml) and the solution was stirred for 1h. The trifluoroacetic acid was evaporated *in vacuo*, the residue was dissolved in DCM (20 ml) and the organic solution was washed with 10% aqueous potassium carbonate, dried over anhydrous magnesium sulfate and the solvent was evaporated to afford colourless foam. The foam was dissolved in 1,2-dichloroethane (5 ml) and cooled to 0°C under argon and aqueous formaldehyde (37%, 0.1 ml, 1.4 mmol), then sodium triacetoxyborohydride (0.26 g, 1.2 mmol) was added and the mixture was stirred for 2h. Saturated sodium hydrogen carbonate solution was added (20 ml) and the product was extracted with DCM (20ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash column chromatography (silica; DCM:methanol:ammonia (880) 90:10:1) to afford colourless foam (0.15g, 67%). ^{1}H NMR ($CDCl_3$) 7.36 (4H, s), 4.19 (2H, s), 3.20 (1H, m), 3.04 (2H, m), 2.50 (1H, m), 2.31 (3H, s), 2.19 (1H, m), 1.86-1.50 (6H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 47.22, H 6.60, N 8.04. $C_{14}H_{22}Cl_2N_2O_2S$ requires C 47.59, H 6.28, N 7.93.

Example 50

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)sulfonamide

Step a *N-(3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl) sulfonamide.* The title compound was prepared as in Example 43 step g with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride. ^{1}H NMR ($CDCl_3$) 7.83 (2H, d), 7.49 (2H, d), 5.80 (1H, bs), 3.73 (1H, bs), 3.30 (2H, m), 3.00 (2H, m), 1.85-1.27 (17H, m).

Step b *N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)sulfonamide* The title compound was prepared as in Example 49 step f with the product from Example 50 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.79 (2H, d), 7.45 (2H, m), 3.12 (1H, m), 3.00 (1H, m), 2.76 (1H, m), 2.24 (3H, s), 2.20 (2H, m), 1.80-1.37 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 47.76, H 6.35, N 8.11. $C_{14}H_{22}Cl_2N_2O_2S$ requires C 47.59, H 6.28, N 7.93.

Example 51

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)methanesulfonamide

Step a *N-(3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)methanesulfonamide.* The title compound was prepared as in Example 49 step e with the product from Example 43 step f replacing the product of Example 49 step d. ^{1}H NMR ($CDCl_3$) 7.36 (4H, s), 5.00 (1H, bs), 4.22 (2H, s), 3.74 (1H, bs), 3.23 (2H, m), 3.04 (2H, m), 1.85-1.27 (17H, m).

Step b *N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)methanesulfonamide.*

The title compound was prepared as in Example 49 step f with the product from Example 51 step b replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.36 (4H, s), 4.18 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.20 (5H, m), 1.73-1.45 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 47.64, H 6.67, N 7.28. $C_{15}H_{24}Cl_2N_2O_2S$-0.6 H_2O requires C 47.58, H 6.72, N 7.40.

Example 52

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-phenylmethanesulfonamide

The title compound was prepared as in Example 51 with phenylmethanesulfonyl chloride replacing (4-chlorophenyl)methanesulfonyl chloride in step a. ^{1}H NMR ($CDCl_3$) 7.40 (5H, m), 4.22 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.19 (3H, s), 2.16 (2H, m), 1.71-1.35 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 51.24, H 7.70, N 8.07. $C_{15}H_{25}ClN_2O_2S$-1.0H_2O requires C 51.31, H 7.76, N 7.98.

Example 53

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-bromophenyl)methanesulfonamide

The title compound was prepared as in Example 51 with (4-bromophenyl)methanesulfonyl chloride[3] replacing (4-chlorophenyl)methanesulfonyl chloride in step a. ^{1}H NMR ($CDCl_3$) 7.50 (2H, m), 7.27 (2H, m), 4.16 (2H, s), 3.03 (2H, m), 2.88 (1H, m), 2.24 (5H, m), 1.75-1.54 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 43.55, H 5.90, N 6.57. $C_{15}H_{24}BrClN_2O_2S$ requires C 43.75, H 5.87, N 6.80.

Example 54

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-(4-chlorophenyl) ethanesulfonamide

The title compound was prepared as in Example 51 with 2-(4-chlorophenyl)ethanesulfonyl chloride[3] replacing (4-chlorophenyl)methanesulfonyl chloride in step a. ^{1}H NMR ($CDCl_3$) 7.29 (2H, m), 7.16 (2H, m), 3.21 (2H, m), 3.09 (4H, m), 2.97 (1H, m), 2.32 (3H, s), 2.23 (2H,m), 1.77-1.41 (8H, m). Found C 55.46, H 7.44, N 8.09. $C_{16}H_{25}ClN_2O_2S$ requires C 55.72, H 7.31, N 8.12.

Example 55

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-3-(4-chlorophenyl)propanesulfonamide

The title compound was prepared as in Example 51 with 3-(4-chlorophenyl)propanesulfonyl chloride[3] replacing (4-chlorophenyl)methanesulfonyl chloride in step a. ^{1}H NMR ($CDCl_3$) 7.31 (2H, m), 7.16 (2H, d), 3.14 (2H, m), 3.00 (3H, m), 2.78 (2H, t), 2.35 (3H, s), 2.28 (2H, m), 2.15 (2H, m), 1.78-1.47 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxane. Found C 51.39, H 7.22, N 7.00. $C_{17}H_{28}Cl_2N_2O_2S$ requires C 51.64, H 7.14, N 7.08.

Example 56

N-(4-(1-Methyl-pyrrolidin-2S-yl)-butyl)-(4-chlorophenyl)methanesulfonamide

The title compound was prepared as in Example 49, steps b-f, with the product from Example 43 step e replacing 2S-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester as the substrate in step b. ^{1}H NMR ($CDCl_3$) 7.36 (4H, m), 4.30 (1H, bs), 4.21 (2H, s), 3.09 (1H, m), 3.00 (2H, t), 2.32 (3H, s), 2.19-1.26 (12H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from

water/dioxane. Found C 50.20, H 6.93, N 7.31. $C_{16}H_{26}Cl_2N_2O_2S$ requires C 50.39, H 6.87, N 7.35.

Example 57

N-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)methanesulfonamide

Step a *5-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentanoic acid ethyl ester.* A solution of triethyl 4-phosphonocrotonate (3.6ml, 16.3mmol) in THF (20ml) was added dropwise to a slurry of sodium hydride (60% dispersion in mineral oil, 0.72g, 18.0mmol) in THF (20ml) at 0°C under an atmosphere of argon. The mixture was allowed to warm to ambient temperature, stirred for 20 mins, then cooled to -20°C and a solution of the product from Example 43 step b in THF (30 ml) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 2h, then it was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic phase was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica; hexane:ethyl acetate 80:20). A round bottom flask containing the purified material (1.9 g), 10% palladium-on-charcoal (0.2 g) and THF:methanol 1:1 (30 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to afford colourless oil (1.85 g, 46%). ^{1}H NMR ($CDCl_3$) 4.12 (2H, q), 3.73 (1H, bs), 3.3 (2H, m), 2.30 (2H, t), 1.91-1.60 (8H, m),1.46 (9H, s), 1.30 (2H, m), 1.25 (3H, t).

Step b *5-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentan-1-ol.* The title compound was prepared as in Example 40 step c with the product of Example 57 step a replacing the product of Example 40 step b.

Step c *5-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentylamine.* The title compound was prepared as in Example 42 step b with the product of Example 57 step b replacing the product of Example 42 step a.

Step d *N-(5-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)methanesulfonamide* . The title compound was prepared as in Example 49 step e with the product of Example 57 step c replacing the product of Example 49 step d.

Step e *N-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)methanesulfonamide* The title compound was prepared as in Example 49 step f with the product from

Example 57 step d replacing thr product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.33 (4H, m), 4.50 (1H, bs), 4.19 (2H, s), 3.06 (1H m), 2.97 (2H, t), 2.29 (3H, s), 2.14 (1H, m), 1.96 (2H, m), 1.66 (3H, m), 1.45 (3H, m), 1.25 (5H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxane. Found C 51.26, H 7.20, N 6.89. $C_{17}H_{28}Cl_2N_2O_2S$ requires C 51.64, H 7.14, N 7.09.

Example 58

N-(3-Pyrrolidin-1-yl-propyl)-(4-chlorophenyl)methanesulfonamide

The title compound was prepared as in Example 49 step e with N-(3-aminopropyl)pyrrolidine replacing the product of Example 49 step d. ^{1}H NMR ($CDCl_3$) 7.36 (4H, s), 4.19 (2H, s), 3.10 (2H, t), 2.60 (2H, t), 2.47 (4H, bs), 1.68 (6H, m). Found C 52.72, H 6.86, N 8.66%; $C_{14}H_{21}ClN_2O_2S$ requires C 53.07, H 6.68, N 8.84%.

Example 59

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

Step a *N-tert-Butoxycarbonyl-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide.* To an ice-cooled solution of chlorosulfonyl isocyanate (0.64ml, 7.4mmol) in DCM (15 ml) was added dropwise a solution of dry *tert*-butanol (1.0 ml, 10.8 mmol) in DCM (10 ml). The solution was allowed to warm to ambient temperature, stirred for 10 min and added dropwise to an ice cooled solution of the product from Example 43 step f (1.3 g, 5.7 mmol) and triethylamine (1.2ml, 8.6mmol) in DCM (20ml). The mixture was stirred for 18h, allowed to warm to ambient temperature. The solution was washed with water (20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography (silica; DCM:ethyl acetate 90:10) of the residue afforded the product as a colourless oil (1.67g, 72%). ^{1}H NMR ($CDCl_3$) 7.63 (1H, s), 5.50 and 5.30 (1H, 2xbs), 3.80 (1H, bs), 3.30 (2H, m), 3.09 (2H, bs), 1.92-1.39 (26H, m).

Step b *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide.* To an ice-cooled solution of N-*tert*-butoxycarbonyl-N'-(3-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide (1.6g, 3.93mmol) and 4-chlorobenzyl bromide (0.8g, 3.90mmol) in dry DMF (10 ml) was added sodium hydride (0.17g, 4.3 mmol, 60% dispersion in oil). The mixture was allowed to warm slowly to ambient temperature over 18h. Water (50ml) was added

and the mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated. Flash column chromatography (silica; DCM:ethyl acetate 95:5) of the residue afforded the product (1.56g, 75%). ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 5.40 and 5.25 (1H, 2xbs), 4.80 (2H, s), 3.75 (1H, bs), 3.29 (2H, m), 2.84 (2H, bs), 1.92-1.39 (26H, m).

Step c *N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide*. The title compound was prepared as in Example 49 step f with the product from Example 59 step b replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 4.50 (1H, bs), 4.18 (2H, s), 3.14 (1H, m), 3.07 (1H, m), 2.89 (1H, m), 2.33 (3H, s), 2.25 (2H, m), 1.79-1.43 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxane. Found C 46.26, H 6.44, N 10.63. $C_{15}H_{25}Cl_2N_3O_2S$. 0.3 mol water requires C 46.46, H 6.65, N 10.84.

Example 60

N-Benzyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

Step a *N-benzyl-N'-(tert-butoxycarbonyl)sulfamide.* The title compound was prepared as in Example 59 step a with benzylamine replacing the product from Example 43 step f.

Step b *N-Benzyl-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide.* To an ice-cooled solution of the product from Example 43 step e (0.9g, 3.9mmol) and N-benzyl-N'(*tert*-butoxycarbonyl)sulfamide (1.22g, 3.9mmol) and triphenylphosphine (1.33g, 5.07mmol) in THF (10ml) was added a solution of diethyl azodicarboxylate (0.87ml, 5.07mmol) in THF (3ml). The yellow solution was allowed to warm to ambient temperature and stirred for 2h. The solvent was evaporated and the residue was purified by flash chromatography (silica; hexane:ethyl acetate 70:30). Thus the product was isolated as a colourless foam (1.7g, 88%). ^{1}H NMR ($CDCl_3$) 7.33 (5H, m), 5.60 (1H, bs), 4.13 (2H, m), 3.80 (1H, bs), 3.59 (2H, m), 3.30 (2H, m), 1.84-1.44 (26H, m).

Step c *N-Benzyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide*. The title compound was prepared as in Example 49 step f with the product from Example 60 step b replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.31 (5H, m), 4.60 (1H, bs), 4.21 (2H, s), 3.23 (1H, m), 3.05 (1H, m), 2.93 (1H, m), 2.40 (3H, s),

2.35 (2H, m), 1.83-1.48 (8H, m). Found C 56.00, H 8.10, N 12.93. $C_{15}H_{25}N_3O_2S$-$0.6H_2O$ requires C 55.90, H 8.20, N 13.04.

Example 61

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)sulfamide

Step a *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2R-yl)-propan-1-ol.* The title compound was prepared as in Example 43 steps a-e with N-(*tert*-butoxycarbonyl)-D-proline replacing N-(*tert*-butoxycarbonyl)-L-proline in step a.

Step b *N-(4-Chlorobenzyl)-N-(tert-butoxycarbonyl)sulfamide.* The title compound was prepared as in Example 59 step a with 4-chlorobenzylamine replacing the product from Example 43 step f.

Step c *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2R-yl)-propyl)sulfamide.* The title compound was prepared as in Example 60 step b using the products derived from Example 61 steps a and b.

Step d *N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 60 step c replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.34 (4H, m), 4.30 (1H, bs), 4.20 (2H, s), 3.08 (2H, m), 2.93 (1H, m), 2.34 (3H, s), 2.27 (2H, m), 1.78-1.50 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 45.93, H 6.66, N 10.74. $C_{15}H_{25}Cl_2N_3O_2S$-$0.53H_2O$ requires C 45.97, H 6.70, N 10.72.

Example 62

N-Cyclohexanemethyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 60 with cyclohexanemethylamine replacing the product from Example 43 step f , in step a. ^{1}H NMR ($CDCl_3$) 4.06 (1H, t), 3.07 (2H, m), 2.98 (1H, m), 2.87 (2H, t), 2.32 (3H, s), 2.23 (2H, m), 1.77-1.46 (14H, m), 1.21 (3H, m), 0.95 (2H m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 47.98, H 9.39, N 11.38; $C_{15}H_{32}ClN_3O_2S$-$1.13H_2O$ requires C 48.13, H 9.23, N 11.22.

Example 63

N-(2-(4-Chlorophenyl)-ethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 60 with 2-(4-chlorophenyl)ethylamine replacing the product from Example 43 step f , in step a.. ^{1}H NMR ($CDCl_3$) 7.28 (2H, m), 7.16 (2H,d), 4.05 (1H, bs), 3.28 (2H, m), 3.12 (1H, m), 2.96 (1H, m), 2.85 (3H, m), 2.31 (3H, s), 2.21 (2H, m), 1.76-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 45.29, H 6.98, N 10.10. $C_{16}H_{27}Cl_2N_3O_2S$-1.47H_2O requires C 45.45, H 7.14, N 9.94.

Example 64

N-(4-Chlorophenyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 60 with 4-chloroaniline replacing the product from Example 43 step f , in step a. ^{1}H NMR ($CDCl_3$) 7.27 (2H, m), 7.12 (2H, m), 3.08 (2H, m), 2.85 (1H, m), 2.26 (2H, m), 2.24 (3H, s), 1.75-1.47 (8H, m). Found C 47.82, H 6.72, N 12.09. $C_{14}H_{22}ClN_3O_2S$-1.0H_2O requires C 48.01, H 6.92, N 12.00.

Example 65

N-(4-Bromobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 59 with 4-bromobenzylbromide replacing 4-chlorobenzylbromide, in step b. ^{1}H NMR ($CDCl_3$) 7.46 (2H, d), 7.23 (2H, d), 4.70 (1H, bs), 4.14 (2H, s), 3.12 (1H, m), 3.02 (1H, m), 2.88 (1H, m), 2.32 (3H, s), 2.24 (2H, m), 1.78-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 41.91, H 6.17, N 9.59. $C_{15}H_{25}BrClN_3O_2S$ requires C 42.21, H 5.90, N 9.85.

Example 66

N-(4-Iodobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 59 with 4-iodobenzylbromide replacing 4-chlorobenzylbromide, in step b. ^{1}H NMR ($CDCl_3$) 7.67 (2H, d), 7.11 (2H, d), 4.50 (1H, bs), 4.15 (2H, s), 3.12 (1H, m), 3.04 (1H, m), 2.90 (1H, m), 2.32 (3H, s), 2.29 (2H, m), 1.78-1.42 (8H, m). Found C 40.77, H 5.79, N 9.41. $C_{15}H_{25}ICIN_3O_2S$-0.35H_2O requires C 40.61, H 5.61, N 9.47.

Example 67

N-(4-Chlorobenzyl)-N'-(2-(1-methyl-pyrrolidin-2S-yl)-ethyl)sulfamide

The title compound was prepared as in Example 59, with the product from Example 49 step d replacing the product of Example 43 step f, in step a. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 4.60 (1H, bs), 4.18 (2H, s), 3.20 (1H, m), 3.05 (2H, m), 2.41 (1H, m), 2.32 (3H, s), 2.18 (1H, m), 1.86-1.58 (6H, m). Found C 50.46, H 6.75, N 12.42. $C_{14}H_{22}ClN_3O_2S$ requires C 50.67, H 6.68, N 12.66.

Example 68

N-(4-Chlorobenzyl)-N'-(4-(1-methyl-pyrrolidin-2S-yl)-butyl)sulfamide

Step a *2S-(4-Amino-butyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.* The title compound was prepared as in Example 49 steps b-d with the product of Example 43 step e replacing the product of Example 49 step a. ^{1}H NMR ($CDCl_3$) 3.70 (1H, m), 3.30 (2H, m), 2.70 (2H, t), 1.86- 1.21 (21H, m).

Step b *N-tert-Butoxycarbonyl-N'-(4-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)sulfamide.* The title compound was prepared as in Example 59 step a with 2S-(4-amino-butyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester replacing the product from Example 43 step f. ^{1}H NMR ($CDCl_3$) 7.50 (1H, bs), 5.17 and 4.50 (1H, 2xbs), 3.75 (1H, bs), 3.30 (2H, m), 3.08 (2H, m), 1.88-1.31 (28H, m).

Step c *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(4-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)sulfamide.* The title compound was prepared as Example 59 step b with N-*tert*-butoxycarbonyl-N'-(4-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)sulfamide replacing the product of Example 59 step a. ^{1}H NMR ($CDCl_3$) 7.32 (4H, m), 5.23 (1H, t), 4.80 (2H, s), 3.78 (1H, bs), 3.31 (2H, m), 2.80 (2H, m), 1.82-1.49 (6H, m), 1.49 (9H, s), 1.46 (9H, s), 1.25 (4H, m).

Step d *N-(4-Chlorobenzyl)-N'-(4-(1-methyl-pyrrolidin-2S-yl)-butyl)sulfamide.* The title compound was prepared as in Example 49 step f with N-(*tert*-butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(4-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)sulfamide replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.33 (4H, m), 4.60 (1H, bs), 4.30 (1H, bs), 4.20 (2H, s), 3.22 (1H, m), 3.03 (2H, t), 2.41 (3H, s), 2.29-1.33 (12H, m). The hydrochloride salt was prepared in dioxane and lyophilised from water/dioxane. Found C 48.11, H 6.92, N 10.29. $C_{16}H_{27}Cl_2N_3O_2S$ requires C 48.48, H 6.87, N 10.60.

Example 69

N-(4-Chlorobenzyl)-N'-(5-(1-methyl-pyrrolidin-2S-yl)-pentyl)sulfamide

Step a *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(5-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)sulfamide.* The title compound was prepared as in Example 60 step b using the products derived from Example 57 step b and Example 61 step b. ^{1}H NMR ($CDCl_3$) 7.33 (2H, m), 7.26 (2H, m), 5.63 (1H, t), 4.12 (2H, d), 3.72 (1H, m), 3.57 (2H, m), 3.30 (2H, m), 1.91-1.24 (30H, m).

Step b *N-(4-Chlorobenzyl)-N'-(5-(1-methyl-pyrrolidin-2S-yl)-pentyl)sulfamide.* The title compound was prepared as in Example 49 step f with N-(*tert*-butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(5-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)sulfamide replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.32 (4H, m), 4.60 (1H, bs), 4.19 (3H, s), 3.05 (1H, m), 3.00 (2H, m), 2.31 (3H, s), 2.16-1.23 (14H, m). Found C 54.33, H 7.61, N 11.04. $C_{17}H_{28}ClN_3O_2S$ requires C 54.60, H 7.55, N 11.24.

Example 70

N-(4-Chlorobenzyl)-N'-(3-(1-(3-(4-chlorophenyl)propyl)-pyrrolidin-2S-yl)-propyl)sulfamide.

The title compound was prepared as in Example 60 with 4-chlorobenzylamine replacing benzylamine in step a, and 3-(4-chlorophenyl)propan-1-al replacing aqueous formaldehyde in step c. ^{1}H NMR ($CDCl_3$) 7.30 (6H, m), 7.20 (2H, d), 4.43 (1H, bs), 4.16 (2H, bs), 3.18 (1H, m), 3.02 (1H, m), 2.89 (1H, m), 2.75-2.50 (3H, m), 2.30 (1H, m), 2.11 (2H, m), 1.87-1.36 (10H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 51.46, H 6.39, N 7.76. $C_{23}H_{32}Cl_3N_3O_2S$-0.9H_2O requires C 51.46, H 6.34, N 7.83%.

Example 71

N-(4-Chlorobenzyl)-N'-(3-(1-(iso-butyl)-pyrrolidin-2S-yl)-propyl)sulfamide

The title compound was prepared as in Example 60 with 4-chlorobenzylamine replacing benzylamine in step a, and *iso*-butyraldehyde replacing aqueous formaldehyde in step c. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 5.60 (1H, bs), 4.54 (1H, bs), 4.43 (1H, bs), 4.17 (2H, bs), 3.16 (1H, m), 3.03 (1H, m), 2.93 (1H, m), 2.42-1.48 (13H, m), 0.91 (6H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 50.59, H 7.39, N 9.81. $C_{18}H_{31}Cl_2N_3O_2S$ requires C 50.94, H 7.36, N 9.90.

Example 72

N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide.

Step a *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-tert-butoxycarbonyl-pyrrolidin-2S-yl)-propyl)sulfamide.* To a solution of of N-(4-chlorobenzyl)-N'-(3-(pyrrolidin-2S-yl)-propyl)sulfamide (1.03g, 2.87mmol) in dioxan (10ml) was added di-*tert*-butyldicarbonate (625mg, 2.87mmol) and the reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure and the residue dissolved in chloroform (50ml) and washed sequentially with water (50ml), aqueous citric acid (10%, 50ml) and brine (50ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). The product was dissolved in DMF (8ml) and cooled in ice. The solution was treated sequentially with iodomethane (0.253ml, 4.06mmol) and sodium hydride (60% dispersion in mineral oil, 185mg, 4.63mmol). The suspension was allowed to warm to ambient temperature over 18h and then water (75ml) was added. The aqueous was extracted with ethyl acetate (75ml) and the organic phase was subsequently washed twice with brine (75ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (3:2 hexane:ethyl acetate) to obtain the title compound (686mg, 52%). ^{1}H NMR ($CDCl_3$) 7.35-7.27 (4H, m), 4.27 (2H, s), 3.77 (1H, m), 3.34-3.21 (4H, m), 2.83 (3H, s), 2.65 (3H, s), 1.94-1.24 (17H, m).

Step b *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 42 step d with the product from Example 72 step a replacing the product of Example 42 step c. ^{1}H NMR ($CDCl_3$) 7.35-7.17 (4H, m), 4.27 (2H, s), 3.24-3.18 (2H, m), 3.01-2.95 (2H, m), 2.89-2.86 (1H, m), 2.83 (3H, s), 2.66 (3H, s), 1.78-1.24 (9H, m).

Step c *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 42 step e with the product from Example 72 step b replacing the product of Example 42 step d. The oil was treated with hydrogen chloride-dioxan and the solvent removed *in vacuo*. ^{1}H NMR ($CDCl_3$-free base) 7.35-7.27 (4H, m), 4.28 (2H, s), 3.21 (2H, t, 7.2), 3.10-3.04

(1H, m), 2.83 (3H, s), 2.63 (3H, s), 2.31 (3H, s), 2.20-1.30 (10H, m). Microanalysis found C 49.41 H 7.60 N 10.18. $C_{17}H_{29}ClN_3O_2S$ requires C 49.75 H 7.37 N 10.24.

Example 73

N-(4-Chlorobenzyl)-N-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

Step a *N-(4-Chlorobenzyl)- N'-(tert-butoxycarbonyl)- N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 60 step b with the products derived from Example 43 step e and Example 61 step b.

Step b *N-(4-Chlorobenzyl)-N-methyl- N'-(tert-butoxycarbonyl)- N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide.* To a solution of N-(4-chlorobenzyl)- N'-(*tert*-butoxycarbonyl)- N'-(3-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)sulfamide (1.0g, 1.9mmol) in DMF (5ml) was added sodium hydride (90mg, 2.26mmol; 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the stirring was continued for 1h. Iodomethane (0.13ml, 2.1mmol) was added and the stirring was continued overnight. Water (50ml) was added and the product was extracted with ethyl acetate (2x30ml), the organic phase was dried, the solvent was evaporated. Flash column chromatography (silica; hexane:ethyl acetate 70:30) afforded the title compound as a colourless foam (0.94g, 91%). ^{1}H NMR ($CDCl_3$) 7.28 (4H, m), 4.39 (2H, s), 3.70 (3H, m), 3.30 (2H, m), 2.75 (3H, s), 1.85-1.26 (26H, m).

Step c *N-(4-Chlorobenzyl)-N-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide* The title compound was prepared as in Example 42 step e with the product from Example 73 step b replacing the product of Example 42 step d. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 4.26 (2H, s), 3.11 (2H, m), 2.95 (1H, m), 2.67 (3H, s), 2.33 (3H, s), 2.22 (2H, m), 1.78-1.44 (12H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan.

Example 74

N-(4-Chlorobenzyl)-N'-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-methyl-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 73 step b with the product from Example 59 step b replacing the product of Example 73 step a. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 4.82 (2H, s), 3.80 (1H, bs), 3.30 (2H, m), 3.13 (2H, m), 2.79 (3H, s), 1.87-1.26 (26H, m).

Step b *N-(4-Chlorobenzyl)-N'-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 75 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.32 (4H, m), 4.50 (1H, m), 4.16 (1H, bs), 3.07 (3H, m), 2.79 (3H, s), 2.30 (3H, s), 1.76-1.29 (10H, m).Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt.

Example 75

N-(4-Chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 74 step a with methyl bromoacetate replacing iodomethane. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 4.821 (2H, s), 4.05 (2H, s), 3.70 (4H, bs), 3.27 (4H, m), 1.87-1.26 (26H, m).

Step b *N-(4-Chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.*

The title compound was prepared as in Example 49 step f with the product from Example 75 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 5.05 (1H, bs), 4.30 (2H, s), 4.08 (2H, s), 3.75 (3H, s), 3.24 (2H, m), 3.09 (1H, m), 2.30 (3H, s), 2.177-1.22 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found 45.81 H 6.61 N 8.90 $C_{18}H_{29}Cl_2N_3O_4S$-0.97H_2O requires C 45.82 H 6.61 N 8.90.

Example 76

N-(4-Chlorobenzyl)-N'-(2-hydroxyethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide. The title compound was prepared as in Example 40 step c with the product from Example 75 step b replacing the product of Example 40 step b. ^{1}H NMR ($CDCl_3$) 7.29 (4H, m), 4.17 (2H, s), 3.67 (3H, m), 3.35 (2H, m), 3.20 (2H, m), 3.02 (1H, m), 2.27 (3H, s), 2.16-1.20 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt.

Example 77

N-(4-Chlorobenzyl)-N'-(3-phthalimido-propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide. To an ice-cooled stirred solution of the product from Example 59 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 1h, whereupon N-(3-bromopropyl)phthalimide (295mg, 1.10mmol) was added. The reaction mixture was heated at 100^{0}C for 2h and then allowed to cool, diluted with water (30ml), extracted twice with ethyl acetate (30ml) and the aqueous phase was discarded. The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue treated with trifluoroacetic acid (5ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was evaporated at reduced pressure and the residue dissolved in DCM (30ml). The organic phase washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (5ml) and treated sequentially with aqueous formaldehyde (37%, 0.20ml) and sodium triacetoxyborohydride (300mg, 1.42mmol). The resultant suspension stirred at ambient temperature for 1h. Quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ^{1}H NMR ($CDCl_3$) 7.83 (2H, m), 7.71 (2H, m), 7.30 (4H, m), 4.75 (1H, bs), 4.15 (2H, s), 3.71 (2H, m), 3.25 (2H, m), 3.16 (2H, m), 3.02 (1H, m), 2.26 (3H, s), 2.10-1.10 (12H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 54.50 H 6.11 N 9.56 $C_{26}H_{34}Cl_2N_4O_4S$ requires C 54.83 H 6.02 N 9.84.

Example 78

N-(4-Chlorobenzyl)-N'-(3-amino-propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide. To a stirred solution of Example 77 (200mg, 0.38mmol) in ethanol (2ml) was added hydrazine hydrate (0.06ml) and the reaction mixture heated at reflux for 1h. The solvent was removed at reduced pressure, the residue was suspended in chloroform (10ml) and the solid removed by filtration. The filtrate was evaporated at reduced pressure and the residue evaporated thrice form chloroform

(10ml) to afford the title compound (125mg, 82%). ^{1}H NMR ($CDCl_3$) 7.28 (5H, m), 4.12 (2H, s), 3.24 (2H, m), 3.2-2.5 (2H, vbs), 3.15 (2H, m), 3.03 (1H, m), 2.72 (2H, m), 2.27 (3H, s), 2.14-1.00 (12H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt.

Example 79

N-(4-Chlorobenzyl)-N'-(methylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(carboxymethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* To a solution of Example 75 step a (3.54g, 5.86mmol) in THF (10ml) was added an aqueous solution of lithium hydroxide (1M, 10ml) and the resultant reaction stirred at ambient temperature for 18h. The solution was evaporated at reduced pressure to half of the initial volume and diluted with aqueous hydrochloric acid (2M, 5ml) and water (50ml). The aqueous phase was extracted twice with ethyl acetate (50ml) and the combined organic layers washed with brine (50ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound. ^{1}H NMR (DMSO-d_6) 13.0 (1H, bs), 7.41(2H, d, 8.4), 7.30 (2H, d, 8.4), 4.75 (2H, s), 4.03 (2H, s), 3.75 (1H, m), 3.18 (4H, m), 2.00-1.10 (22H, m).

Step b *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(methylamidomethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* To an ice-cooled solution of the product from Example 79 step a (590mg, 1.00mmol) in DCM (20ml) was added N-hydroxysuccinimide (126mg, 1.10mmol). The coolant was removed and the reaction stirred at ambient temperature and treated with dicyclohexylcarbodiimide (233mg, 1.11mmol) and stirred at this temperature for 1h. The suspension was filtered to remove the solid and methylamine was bubbled through the filtrate for 5 minutes. The reaction mixture was stirred at ambient temperature for a further 1h and then diluted with DCM (20ml). The reaction mixture washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric (1M, 20ml) and water (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure to afford the title compound (650mg, q). ^{1}H NMR ($CDCl_3$) 7.31 (4H, m), 6.70 (1H, bs), 4.84 (2H, s), 3.91 (2H, s), 3.70 (1H, m), 3.30-3.17 (4H, m), 2.81 (3H, d, 4.5), 1.47 (18H, s), 1.90-1.18 (10H, m).

Step c *N-(4-Chlorobenzyl)-N'-(methylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 79 step b replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 6.50(1H, m), 4.69 (1H, s), 4.23 (2H, s), 3.85 (2H, s), 3.17 (2H, m), 3.03 (1H, m), 2.80 (3H, 5.8), 2.28 (3H, s), 2.17-1.00 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 46.63 H 7.04 N 11.93 $C_{18}H_{30}Cl_2N_4O_3S$-$0.5H_2O$ requires C 46.75 H 6.76 N 12.11.

Example 80

N-(4-Chlorobenzyl)-N'-(dimethylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(dimethylamidomethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 79 step b with dimethylamine replacing methylamine. ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 4.80 (2H, s), 4.06 (2H, bs), 3.70 (1H, m), 3.30 (4H, m), 2.91 (6H, m), 1.47 (9H, s), 1.45 (9H, s), 1.91-1.12 (10H, m).

Step b *N-(4-Chlorobenzyl)-N'-(dimethylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 80 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.29 (4H, m), 6.25(1H, m), 4.30 (2H, d, 5.4), 4.14 (2H, s), 3.24 (2H, m), 3.04 (1H, m), 2.96 (3H, s), 2.93 (3H, s), 2.28 (3H, s), 2.15-1.00 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 48.48 H 7.18 N 11.67 $C_{19}H_{32}Cl_2N_4O_3S$ requires C 48.81 H 6.90 N 11.98.

Example 81

N-(4-Chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* To an ice-cooled solution of the product of Example 79 step a (590mg, 1.00mmol), 4-chlorobenzylamine (0.133ml, 1.10mmol), N-hydroxybenzotriazole hydrate (168mg, 1.10mmol) and 4-dimethylaminopyridine (20mg, 0.16mmol) in DCM (20ml) was

added EDC (211mg , 1.10mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 16h. The reaction mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric acid (1M, 20ml) and water (20ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure to afford the title compound (675mg, 95%). ^{1}H NMR ($CDCl_3$) 7.30 (9H, m), 4.83 (2H, s), 4.42 (2H, d, 6), 3.98 (2H, s), 3.60 (1H, m), 3.50-3.00 (4H, m), 1.45 (9H, s), 1.42 (9H, s), 2.0-1.0 (8H, m).

Step b *N-(4-Chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 81 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.32-7.16 (9H, m), 6.81 (1H, m), 4.36 (2H, d, 6), 4.19 (2H, s), 3.84 (2H, s), 3.15 (2H, m), 3.00 (1H, m), 2.24 (3H, s), 2.13-1.00 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 51.22 H 6.10 N 10.04 $C_{24}H_{33}Cl_3N_4O_3S$ requires C 51.11 H 6.10 N 9.93.

Example 82

N-(4-Chlorobenzyl)-N'-(benzyloxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.

Step a *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(benzyloxycarbonylmethyl)-N'(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 74 step a with benzyl bromoacetate replacing iodomethane. ^{1}H NMR ($CDCl_3$) 7.38-7.27 (9H, m), 5.15 (2H, s), 4.78 (2H, s), 3.75 (1H, m), 3.50-3.00(4H, m), 1.49 (9H, s), 1.44 (9H, s), 1.81-1.26 (10H, m).

Step b *N-(4-Chlorobenzyl)-N'-(benzyloxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 81 step a replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.39-7.25 (9H, m), 5.18 (2H, s), 4.26 (2H ,d, 6), 4.11 (2H, s), 3.27 (2H, m), 3.08 (1H, m), 2.31 (3H, s), 2.18-1.00 (10H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 47.70 H 6.99 N 6.74 $C_{24}H_{33}Cl_2N_3O_4S$-$4H_2O$ requires C 47.84 H 6.86 N 6.97.

Example 83

N-(4-Chlorobenzyl)-N'-(3-(4-chlorophenyl)propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)sulfamide. To an ice-cooled stirred solution of the product of Example 59 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed and 3-(4-chlorophenyl)propylmesylate (261mg, 1.10mmol) added. The reaction mixture was heated at 100°C for 3h and then allowed to cool. The reaction mixture was diluted with water (30ml) and extracted with ethyl acetate (30ml). The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (5:4:1 Hexane:DCM:ethyl acetate). The purified material was treated with trifluoroacetic acid (2ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was evaporated at reduced pressure and the residue dissolved in DCM (30ml). The organic phase was washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (3ml) and treated sequentially with aqueous formaldehyde (37%, 0.06ml) and sodium triacetoxyborohydride (160mg, 0.75mmol). The resultant suspension was stirred at ambient temperature for 1h, then quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ^{1}H NMR ($CDCl_3$) 7.32-7.08 (8H, m), 4.62 (1H, bs), 4.12 (2H, s), 3.12 (4H, m), 3.04 (1H, m), 2.59 (2H, m), 2.15 (3H, s), 2.20-1.20 (12H, m). Treatment with hydrogen chloride-dioxan and lyophilisation from water afforded the hydrochloride salt. Microanalysis found C 53.62 H 6.41 N 7.55 $C_{24}H_{34}Cl_3N_3O_2S$ requires C 53.88 H 6.41 N 7.85.

Example 84

N-(4-Chlorobenzyl)-N'-(3-(4R-hydroxy-1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

Step a *2S-(Methoxy-methyl-carbamoyl)- 4R-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester.* The title compound was prepared as in Example 43 step a with N-(*tert*-butoxycarbonyl)-L-*trans*-4-hydroxyproline replacing with N-(*tert*-butoxycarbonyl)-L-proline. ^{1}H NMR (DMSO-d_6) 5.01 (1H, d), 4.64 (1H, m), 4.22

(1H, bs), 3.71 and 3.68 (3H, 2xs), 3.30 (2H, m), 3.10 and 3.08 (3H, 2xs), 2.20 (1H, m), 1.78 (1H, m), 1.37 and 1.31 (9H, 2xs).

Step b *2S-Formyl-4R-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester.* The title compound was prepared as in Example 43 step b with the product from Example 84 step a replacing the product of Example 43 step a. ^{1}H NMR ($CDCl_3$) 9.45 and 9.44 (1H, 2xbs), 4.49 (1H, bs), 4.13 and 4.11 91H, 2xm), 3.58 (2H, m), 2.16-1.97 (3H, m), 1.48 and 1.44 (9H, 2xs).

Step c *3-(1-(tert-Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-acrylic acid ethyl ester.* The title compound was prepared as in Example 43 step c with the the product from Example 84 step b replacing the product of Example 43 step b. ^{1}H NMR (DMSO-d_6) 6.80 (1H, dd), 5.86 (1H, d), 4.50 (1H, bs), 4.30 (1H, m), 4.16 (2H, m), 3.53 (2H, m), 2.17 (1H, m), 1.87 (2H, m), 1.43 (9H, s), 1.26 (3H, t).

Step d *3-(1-(tert-Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propionic acid ethyl ester.* The title compound was prepared as in Example 43 step d with the the product from Example 84 step c replacing the product of Example 43 step c. ^{1}H NMR ($CDCl_3$) 4.40 (1H, m), 4.11 (2H ,m), 3.97 (1H, m), 3.94 (2H, m), 2.28 (2H, t), 2.07 (2H, m), 1.78 (3H, m), 1.47 (9H, s), 1.25 (3H, t).

Step e *3-(1-(tert-Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 40 step c with the the product from Example 84 step d replacing the product of Example 40 step b. ^{1}H NMR (DMSO-d_6) 4.80 (1H, d), 4.35 (1H, t), 4.15 (1H, m), 3.72 (1H, m), 3.35 (2H, m), 3.23 (2H, m), 1.90-1.50 (4H, m), 1.38 (9H, s), 1.16 (2H, m).

Step f *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 60 step b using the products derived from Example 61 step b and Example 84 step e. ^{1}H NMR (DMSO-d_6) 8.26 (1H, s), 7.33 (4H, m), 4.81 (1H, d), 4.06 (3H, m), 3.68 (1H, m), 3.30 (2H, m), 1.90-1.22 (24H, m).

Step g *N-(4-Chlorobenzyl)-N'-(3-(4R-hydroxy-1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 84 step f replacing the product of Example 49 step e. The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan.^{1}H NMR (DMSO-d_6) 10.60 (1H, bs), 7.39 (5H, m), 6.98 (1H, t), 5.50 (1H, bs), 4.33 (1H, bs), 4.01 (2H, d), 3.72 (1H, m), 3.45 (1H, m), 3.30 (1H, m), 2.83 (5H, m), 2.07-1.45 (6H, m).

Example 85

N-(4-Chlorobenzyl)-N'-(3-(4R-(4-chlorobenzyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide

Step a *3-(1-(tert-Butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propionic acid ethyl ester.* To a solution of the product from Example 84 step d (0.90g, 3.13mmol) in DMF (10 ml) was added sodium hydride (0.15g, 3.76mmol, 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the mixture was stirred for 1h, 4-chlorobenzyl bromide was added and the stirring was continued for 16h. The reaction was quenched with water (40ml) and the product was extracted with ethyl acetate (2x20ml), the organic extracts were dried over anhydrous magnesium sulfate, the solvent was evaporated. Purification by flash column chromatography (silica; hexane:ethyl acetate 70:30) afforded the product as a colourless oil (0.36g, 28%). ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 4.50 (2H, m), 4.11 (3H, m), 3.96 (1H, m), 3.70 and 3.50 (1H, 2xbs), 3.67 (1H, bs), 2.28 (2H, m), 2.12 (2H, m), 1.76 (2H, m), 1.47 and 1.45 (9H, 2xs),1.25 (3H, t).

Step b *3-(1-(tert-Butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 40 step c with the product from Example 85 step a replacing the product of Example 40 step b. ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 4.46 (2H, bs), 4.10 (1H, m), 3.96 (1H, bs), 3.67 (3H, m), 3.39 (1H, m),2.13 (1H, m), 1.82 (5H, m), 1.42 (11H, m).

Step c *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 60 step b using the products derived from Example 61 step b and Example 85 step b. ^{1}H NMR ($CDCl_3$) 7.30 (8H, m), 5.70 (1H, bs), 4.45 (2H, bs), 4.12 (2H, d), 4.06 (1H, m), 3.96 (1H, bs), 3.60 (2H, m), 3.30 (1H, m), 1.90-1.22 (24H, m).

Step d *N-(4-Chlorobenzyl)-N'-(3-(4R-(4-chlorobenzyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide.* The title compound was prepared as in Example 49 step f with the product from Example 84 step c replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.30 (8H, m), 4.63 (1H, bs), 4.43 (2H, m), 4.18 (2H, d), 4.11 (1H, m), 3.52 (1H, m), 3.04 (1H, m), 3.04 (1H, m), 2.92 (1H, m), 2.63 (1H, m), 2.43 (1H, m), 2.41 (3H, s), 2.20 (1H, bs),1.97 (1H, m), 1.77 (1H, m), 1.55 (3H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan.

Found C 50.08, H 5.81, N 8.03. $C_{22}H_{30}Cl_3N_3O_3S$-0.2H_2O requires C 50.13, H 5.83, N 7.97.

Example 86

N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)sulfamide. To an ice-cooled solution of of the product from Example 61 step b (321mg, 1.00mmol), 1-(2-hydroxyethyl)pyrrolidine (0.152ml, 1.30mmol) and triphenylphosphine (393mg, 1.50mmol) in THF (2ml) was added in a single portion diethylazodicarboxylate (0.257ml, 1.50mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (25ml) and washed sequentially with water (20ml), twice with aqueous hydrochloric acid (2M, 25ml) and brine (25ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was dissolved in dioxan (5ml) and treated with aqueous hydrochloric acid (2M, 5ml). The resultant mixture was heated at reflux for 1h and then diluted with further aqueous hydrochloric acid (30ml). The aqueous was washed twice with diethyl ether (30ml) and then the pH was adjusted to 11 with ammonia (880). The now basic phase was extracted twice with chloroform (50ml) and then dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (200:10:1 DCM:methanol:ammonia) to afford the title compound as a white solid (95mg, 30%). ^{1}H NMR ($CDCl_3$) 7.35-7.28 (4H, m), 6.0-4.5 (2H, bs), 3.19 (2H, t, 5.7), 2.59 (2H, t, 5.7), 2.50-2.46 (4H, m), 1.73-1.67 (4H, m). Microanalysis found C 49.05 H 6.36 N 13.09 $C_{13}H_{20}ClN_3O_2S$ requires C 49.13 H 6.34 N 13.22.

Example 87

N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)sulfamide. A solution of 4-chlorobenzylamine (0.610ml, 5.00mmol), 1-(3-aminopropyl)pyrrolidine (0.632ml, 5.00mmol) and sulfamide (480mg, 4.99mol) was heated at reflux for 2h. The reaction was allowed to cool and partitioned between ethyl acetate (20ml) and water (20ml). The aqueous was discarded and the organic phase washed with water (20ml) and brine (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (100:10:1 DCM:methanol) to obtain the title compound as a white

solid (365mg, 22%). ^{1}H NMR ($CDCl_3$) 7.35-7.28 (4H, m), 4.18 (2H, s), 3.15 (2H, t, 6), 2.61 (2H, t, 6), 2.51 (4H, bm), 1.82-1.67 (6H, m). Microanalysis found C 49.97 H 6.73 N12.50 $C_{14}H_{22}ClN_3O_2S$-0.26H_2O requires C 49.96 H 6.74 N 12.49.

Example 88

N-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-1-butanesulfonamide

Step a N-*(4-Chlorobenzyl)-methanesulfonamide.* A solution of 4-chlorobenzylamine (12.20g, 86.2mmol) and triethylamine (14.4ml, 103.5mmol) in DCM (200ml) was cooled in an ice bath. Mesyl chloride (7.34ml, 94.9mmol) was added dropwise and the solution was stirred for 10min. The cold bath was removed and the solution stirred for a further 2h. The reaction was diluted with a equal volume of DCM and washed with 10% citric acid solution and brine. The solvent was evaporated and the residue recrystallised from hot ethyl acetate. The product was thus obtained as a colourless crystalline solid (15.34g, 81%).

Step b *N-(tert-Butoxycarbonyl)-N-(4-chlorobenzyl)-methanesulfonamide.* To a solution of N-(4-chlorobenzyl)-methanesulfonamide (15.30g, 69.6mmol) and di-*tert*-butyl-dicarbonate (18.27g, 83.6mmol) in DCM (150ml) was carefully added *N,N*-dimethylaminopyridine (848mg, 6.96mmol); there was immediate and vigorous effervescence. The solution was stirred for 30min, by which time effervescence had ceased. The solution was diluted to a total volume of 500ml with DCM and washed twice with 10% citric acid solution and then brine. The solvent was evaporated to give a yellow solid, which was recrystallised from hot propan-2-ol (100ml). The precipitate was collected by filtration and dried *in vacuo* at 50°C to afford the product as a colourless crystalline solid (19.70g, 89%).

Step c *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propan-1-al.* A solution of oxalyl chloride (1.2ml, 13.7mmol) in DCM (40ml) was cooled to -78°C and dimethylsulfoxide (1.9ml, 27.3mmol) was added dropwise with concomitant effervescence. The solution was stirred for 5 mins, by which time effervescence had ceased, and a solution of the product from Example 43 step e (2.6g, 11.4mmol) in DCM (30ml) was added. The solution was stirred for 20 mins, triethylamine (5.7ml, 41.0mmol) was added, the cold bath was removed and the resultant solution was stirred for 3h. The solution was washed with water (2x50ml), the organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography

(silica; hexane:ethyl acetate 70:30) to afford the aldehyde as an oil (2.16 g, 83%). ^{1}H NMR ($CDCl_3$) 9.77 (1H, t), 3.83 (1H, m), 3.30 (2H, m), 2.46 (2H, m), 1.99-1.26 (15H, m).

Step d *N-(4-Chlorobenzyl)-4-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-1-but-1-enesulfonamide.* A solution of N-(*tert*-butoxycarbonyl)-N-(4-chlorobenzyl)-methanesulfonamide (0.8g, 3.0mmol) in THF (10 ml) was cooled to -78°C, 1.0M potassium *tert*-butoxide (5.0ml, 5.0mmol) was added dropwise and the solution was stirred for 1h. A solution of the aldehyde from step c of this example (0.57g, 2.5mmol) in THF (10ml) was added and the solution was stirred overnight allowing the temperature to slowly warm to ambient temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30ml) and extracted with diethyl ether (2x15ml). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Flash column chromatography (silica; hexane:ethyl acetate 1:1) of the residue gave the product as a colourless foam (0.65g, 62%). ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 6.75 (1H, m), 6.20 (1H, d), 4.74 (1H, m), 4.17 (2H, d), 3.77 (1H, m), 3.30 (2H, m), 2.20 (2H, m), 1.95-1.46 (15H, m).

Step f *N-(4-Chlorobenzyl)-4-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-1-butane sulfonamide.* A round bottom flask containing N-(4-chlorobenzyl)-4-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2S-yl)-1-but-1-enesulfonamide (0.27g, 0.63mmol), 10% palladium-on-charcoal (30mg) and THF:methanol 1:1 (10ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to afford the product as a colourless foam (0.21g, 78%). ^{1}H NMR ($CDCl_3$) 7.32 (4H, m), 5.10 and 4.90 (1H, 2xbs), 4.27 (2H d), 3.75 (1H, m), 3.30 (2H ,m), 2.90 (2H ,m), 1.80-1.26 (19H, m).

Step g *N-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-1-butanesulfonamide.* The title compound was prepared as in Example 49 step f with the product from Example 88 step f replacing the product of Example 49 step e. ^{1}H NMR ($CDCl_3$) 7.30 (4H, m), 5.00 (1H bs), 4.27 (2H, d), 3.05 (1H, m), 2.92 (2H, m), 2.29 (3H, s), 2.16-1.22 (12H, m). The hydrochloride salt was prepared with hydrogen chloride-dioxan and lyophilised from water/dioxan. Found C 47,36, H6.91, N 6.92. $C_{16}H_{26}Cl_2N_2O_2S$-$1.3H_2O$ requires C 47.56, H 7.11, N 6.93%.

References

1. J. Med. Chem. **35**(1): 39 (1992)
2. J. Med. Chem. **37**: 314 (1994)
3. WO97/29092

Histamine H_3 functional assay - guinea pig ileum

The biological activity of the compounds of the examples was measured using the ileal longitudinal muscle, myenteric plexus assay described by Paton and Aboo Zar (*J. Physiol.* 1968, **194**, 13-33). Male Dunkin-Hartley guinea pigs (250-300g) were employed. Briefly, a 50cm portion of ileum proximal to the caecum was removed, after discarding the terminal 20cm. Ileal segments (3cm) were cleaned by passing Krebs-Henseleit buffer containing 3μM mepyramine gently through the ileum using a Pasteur pipette (size: 13.8cm length, 0.65cm diameter). To avoid unnecessary damage to the tissue, Krebs-Henseleit buffer was passed through the ileal segment, while it was lying horizontally on a petri dish. Therefore, the ileum was not over-distended and the buffer flowed through with ease. Each segment was then passed over a Pasteur pipette and the longitudinal muscle layer and adhering myenteric plexus was teased away using moist cotton wool, by stroking tangentially away from the mesenteric attachment. The tissues were suspended in 20ml organ baths containing Krebs-Henseleit buffer at 37±1°C and gassed with 95%CO_2/5%O_2. The tissues were ligated to two parallel stainless steel wires, situated between two platinum electrodes (0.76cm length, 0.06cm diameter). All measurements were recorded isometrically (Grass FTO3 transducer). Following an initial loading tension of 1g, the tissues were stimulated with electrical pulses at a frequency of 0.1Hz and a pulse duration of 0.5msec, as described by Kosterlitz & Watt (*Br. J. Pharmacol.* 1968, 266-276). Initially, the tissues were stimulated at supramaximal (1.3 fold times maximal) voltage for a period of 30 min and then the tissues were washed and re-stimulated. A "sighter dose" of the selective histamine H_3-receptor agonist, R-(α)-methylhistamine (0.3μM) (Arrang *et al. Nature*, 1987, 117-123), was administered. Upon generation of response, the "sighter dose" was removed from the tissues by "washout" (6 washes over 60 min) and during this period the electrical stimulation was switched off. The tissues were then re-stimulated and allowed to stabilise prior to the addition of drug treatments, which were allocated on a randomised block basis to the

organ baths. Following the incubation period, a single cumulative E/[A] curve was obtained. The experimental E/[A] curve data was expressed as the percentage inhibition of the peak height of electrically-stimulated contraction. Antagonist affinity values were calculated from the degree of rightward shift of the R-(α)-methylhistamine E/[A] curves using Schild's methods (Arunlakshana & Schild *Br. J. Pharmacol.* 1959, 48-58). Typical variance in this assay is ± 0.15 log units.

The compounds of the invention were also tested in a guinea pig cortex binding assay, as follows:

Histamine H_3 radioligand binding assay - guinea pig cortex

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The whole brain was removed and immediately placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C). The cortex was dissected, weighed and homogenised in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) (50ml/guinea-pig cortex) using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x 3s). The homogenate was centrifuged at 100 x g for 5min and the supernatants pooled and stored at 4°C. The pellets were rehomogenised in fresh ice-cold buffer (80ml) and recentrifuged (100 x g for 5min). The supernatants were pooled and pellets rehomogenised and recentrifuged (100 x g for 5min). All supernatants were pooled and centrifuged at 39,800 x g for 12 min at 4°C. The final pellet was resuspended in 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) to a tissue concentration of 7.5mg.ml^{-1},using a teflon-in-glass homogeniser.

Incubation conditions

Guinea pig cortex membranes (400µl) were incubated for 165 min at 21±3°C in a final volume of 500µl with 20mM Hepes-NaOH buffer containing [^{3}H]-R-α-methylhistamine (50µl; 1nM) and competing compound. Total and non-specific binding of [^{3}H]-R-α-methylhistamine were defined using 50µl of buffer and 50µl of 10µM thioperamide, respectively. The assay was terminated by rapid filtration through Whatman GF/B filters, presoaked (2hr) in 0.1% polyethyleneimine, using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH6.9 at 21±3°C),

transferred into scintillation vials, 5ml liquid scintillation cocktail was added and after 4 hours the bound radioactivity was determined by counting (4 min) in a Beckman liquid scintillation counter.

Data analysis

Data are analysed using GraphPad prism and the general equation for a competition curve with variable Hill slope (n_H).

$$Y = \text{Non-specific binding} + \frac{\text{(Total binding - Non-specific binding)}}{1+10^{((\log IC_{50}-X).n_H)}}$$

where

X is the log concentration of competing compound,

Y is the binding obtained at each concentration of X,

pIC_{50} is the concentration of the competitor required to compete for half of the specific binding.

The IC_{50} is converted to the K_I using the Cheng Prusoff equation,

$$K_I = IC_{50}/(1+(L/K_D))$$

where

IC_{50} is the concentration of competitor required to compete for half the specific binding,

L is the radioligand concentration used,

K_D is the equilibrium dissociation constant for the radioligand determined by saturation experiments.

The results obtained from the functional and binding assays described above are set out in Table 1 below:

Table 1

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
1	7.2	5.4
2	7.5	6.4

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
3	7.1	6.1
4	7.2	6.5
5	7.0	6.1
6	7.4	6.4
7	7.4	6.4
8	7.5	6.2
9	8.3	6.5
10	7.6	6.5
11	7.4	6.3
12	6.3	6.3
13	6.8	5.4
14	8.3	7.3
15	8.3	7.3
16	7.4	6.0
17	9.1	6.7
18	7.3	6.8
19	7.1	6.7
20	6.5	5.5
21	8.2	7.1
22	8.0	7.1
23	7.1	6.6
24	7.6	6.4
25	7.5	N/T
26	8.4	7.4
27	9.0	7.5
28	7.5	6.7
29	8.5	7.7
30	7.4	6.8
31	7.0	5.4
32	6.1	N/T
33	6.9	5.9

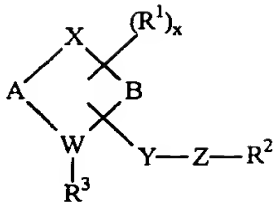
Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
34	6.5	6.0
35	6.6	6.2
36	6.3	6.1
37	6.8	N/T
38	5.6	N/T
39	5.9	N/T
40	6.2	5.9
41	7.0	6.2
42	5.9	N/T
43	6.9	6.3
44	5.7	N/T
45	5.5	N/T
46	5.6	N/T
47	5.8	N/T
48	5.8	N/T
49	5.8	5.5
50	6.1	6.1
51	6.7	6.5
52	6.7	6.3
53	6.6	6.0
54	7.2	6.5
55	6.9	6.5
56	6.4	6.4
57	6.4	6.3
58	6.0	6.2
59	7.0	6.8
60	5.8	N/T
61	6.7	N/T
62	6.3	5.6
63	5.8	N/T
64	6.4	5.8

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
65	7.0	6.7
66	6.5	7.0
67	6.3	6.4
68	6.9	6.7
69	7.1	N/T
70	5.8	N/T
71	7.8	5.7
72	6.3	6.3
73	6.5	6.0
74	6.9	6.5
75	6.6	5.5
76	5.9	N/T
77	6.5	<5.5
78	6.0	5.5
79	5.7	5.7
80	5.5	N/T
81	6.1	N/T
82	5.3	N/T
83	6.0	<5.5
84	6.9	5.8
85	5.6	<5.5
86	6.0	N/T
87	6.5	6.2
88	6.5	6.5

N/T= not tested

CLAIMS

1. A compound of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

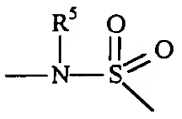
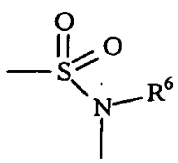
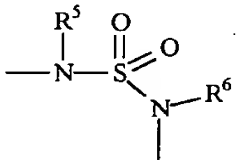
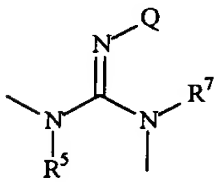
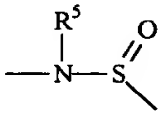
R^3 is absent when -Y-Z-R^2 is attached to W, or is C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

Y is C_2 to C_{10} alkylene and replaces a hydrogen atom on any of A, B, W and X; and

Z is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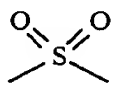


wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which one hydrogen atom may be replaced by halogen, and Q is H, methyl or -CN, or Q is linked to R^5 or R^7 to form a five-membered ring,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^2 is selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo.

3. A compound according to claim 1 wherein R^2 is selected from phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, toluyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

4. A compound according to any of claims 1 to 3 wherein x is 0.

5. A compound according to any of claims 1 to 3 wherein x is 1 or 2, and R^1 is selected from hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

6. A compound according to any preceding claim wherein R^3 is H, C_1 to C_7 alkyl or benzyl

7. A compound according to any preceding claim wherein R^5, R^6 and R^7 are independently selected from H, aryl(C_1 to C_3)alkyl and cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

8. A compound according to any preceding claim wherein Y is ethylene, propylene, butylene, pentylene, hexylene or heptylene.

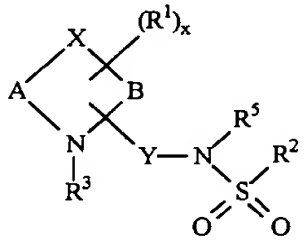
9. A compound according to any preceding claim wherein $m+n \geq 3$.

10. A compound according to any preceding claim, for use in therapy.

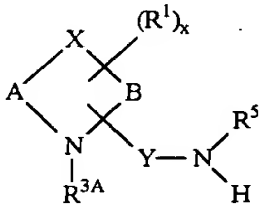
11. A compound which is degraded *in vivo* to yield a compound according to any of claims 1 to 9.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 9, and a physiologically acceptable diluent or carrier.

13. A method of making a compound of the formula

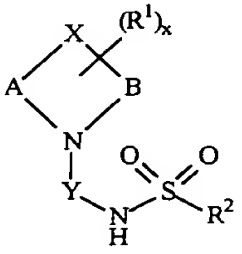


wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula R^2SO_2Cl with a compound of the formula

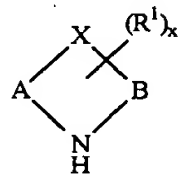


wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group.

14. A method of making a compound of the formula

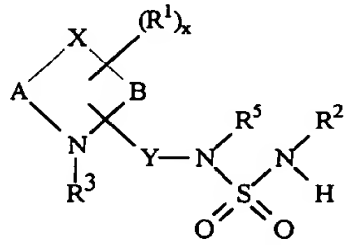


wherein A, B, x, R^1, R^2, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

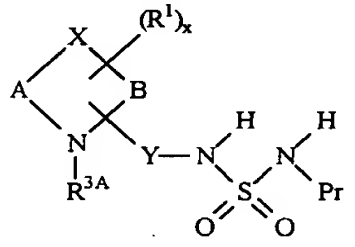


with a compound of the formula Cl-Y-NH-SO_2-R^2.

15. A method of making a compound of the formula

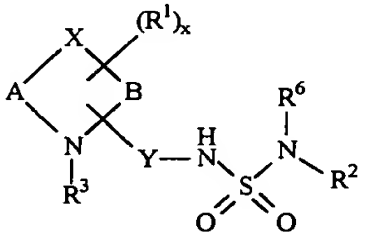


wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

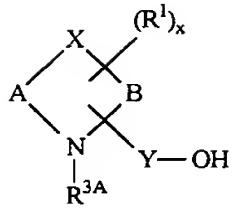


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group and Pr is a protecting group) with a compound of the formula R^2Br, and reacting the product with R^5Br when R^5 is not hydrogen.

16. A method of making a compound of the formula

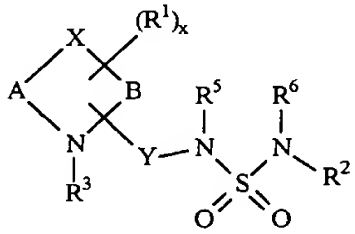


wherein A, B, x, R^1, R^2, R^3, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

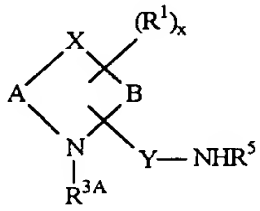


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2-NH-SO_2-NH-Pr, wherein Pr is a protecting group, and reacting the product with R^6Br when R^6 is not hydrogen.

17. A method of making a compound of the formula

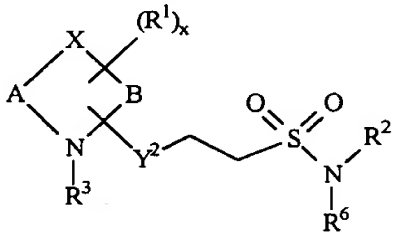


wherein A, B, x, R^1, R^2, R^3, R^5, R^6, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

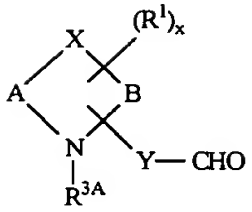


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2R^6NH and sulfamide.

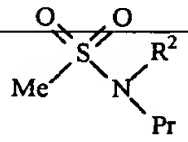
18. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^3, R^6 and X are as recited in claim 1 and Y^2 is a bond or C_1 to C_8 alkylene, said method comprising the step of reacting a compound of the formula

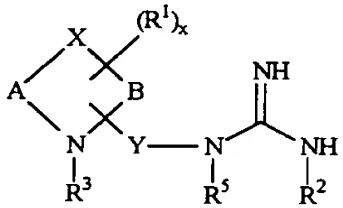


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula

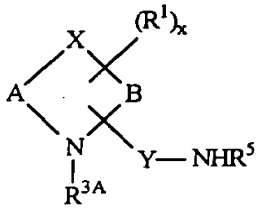


wherein Pr is a protecting group, reducing the reaction product, and (when R^6 is not hydrogen) reacting the reduced product with R^6Br.

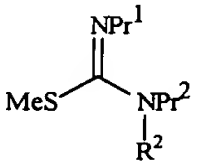
19. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

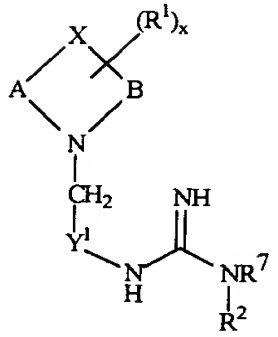


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula

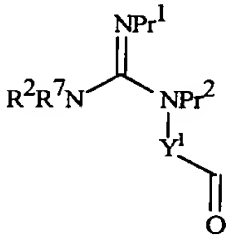


wherein Pr^1 and Pr^2 are protecting groups.

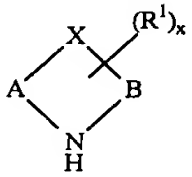
20. A method of making a compound of the formula



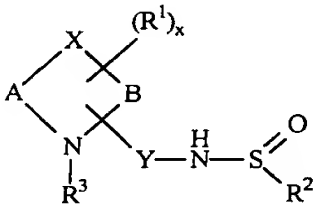
wherein A, B, x, R^1, R^2, and X are as recited in claim 1 and Y^1 is a C_1 to C_9 alkylene group, said method comprising the step of reacting a compound of the formula



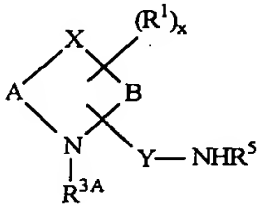
(wherein Pr^1 and Pr^2 are protecting groups) with a compound of the formula



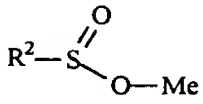
21. A method of making a compound of the formula



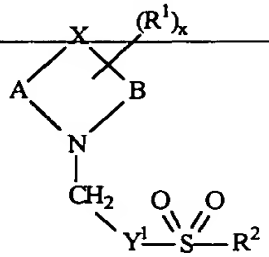
wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



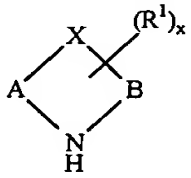
(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula



22. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, and X are as recited in claim 1 and Y^1 is a C_1 to C_9 alkylene group, said method comprising the step of reacting a compound of the formula



with a compound of the formula R^2-SO_2-Y^1-CHO.

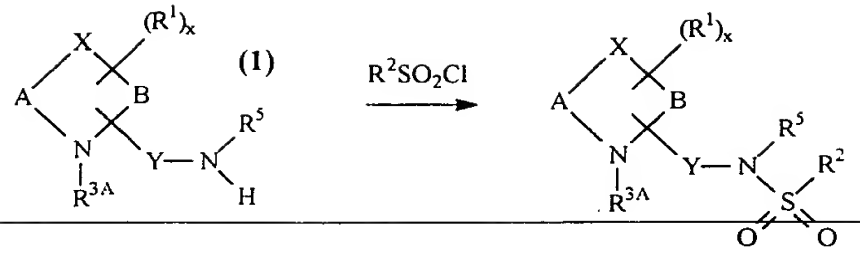


Figure 1

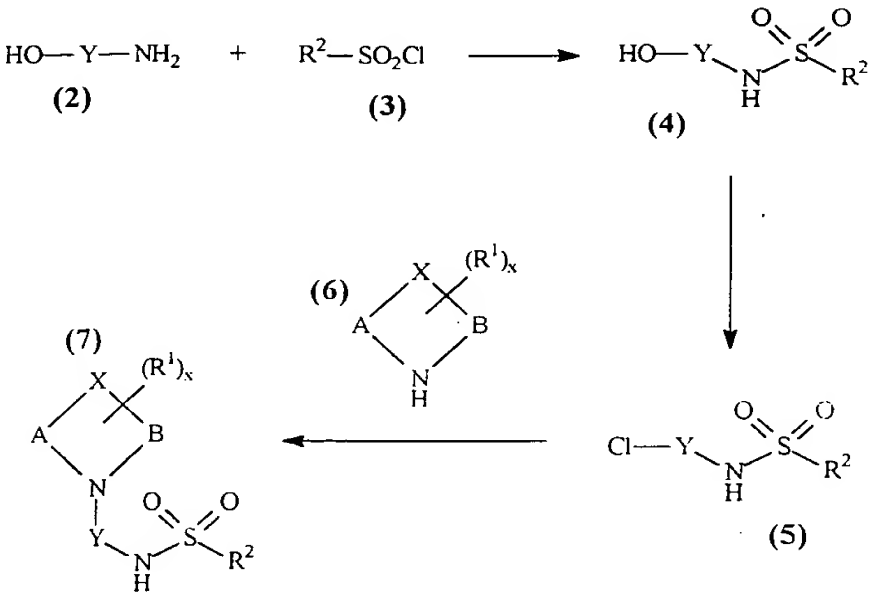


Figure 2

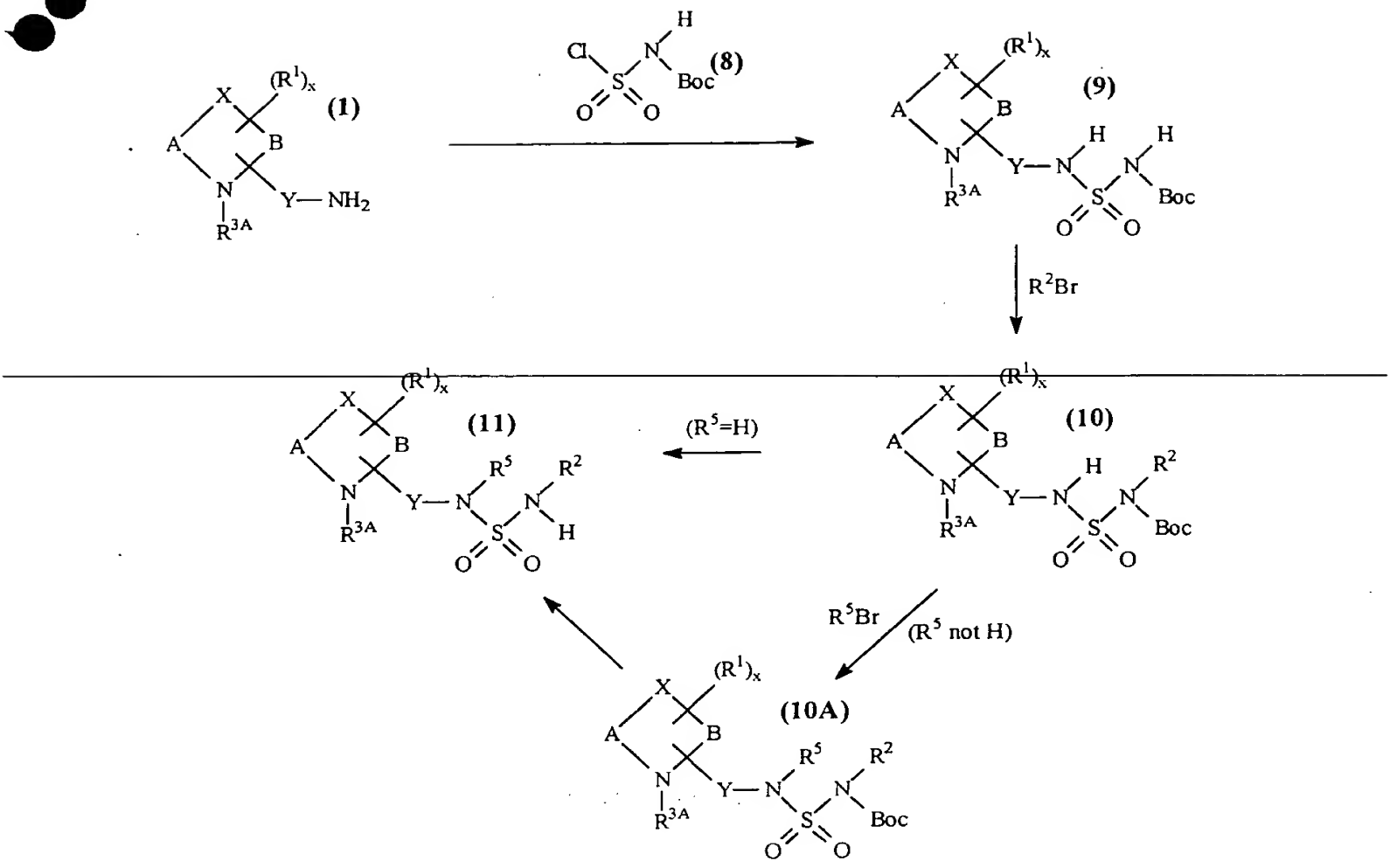


Figure 3

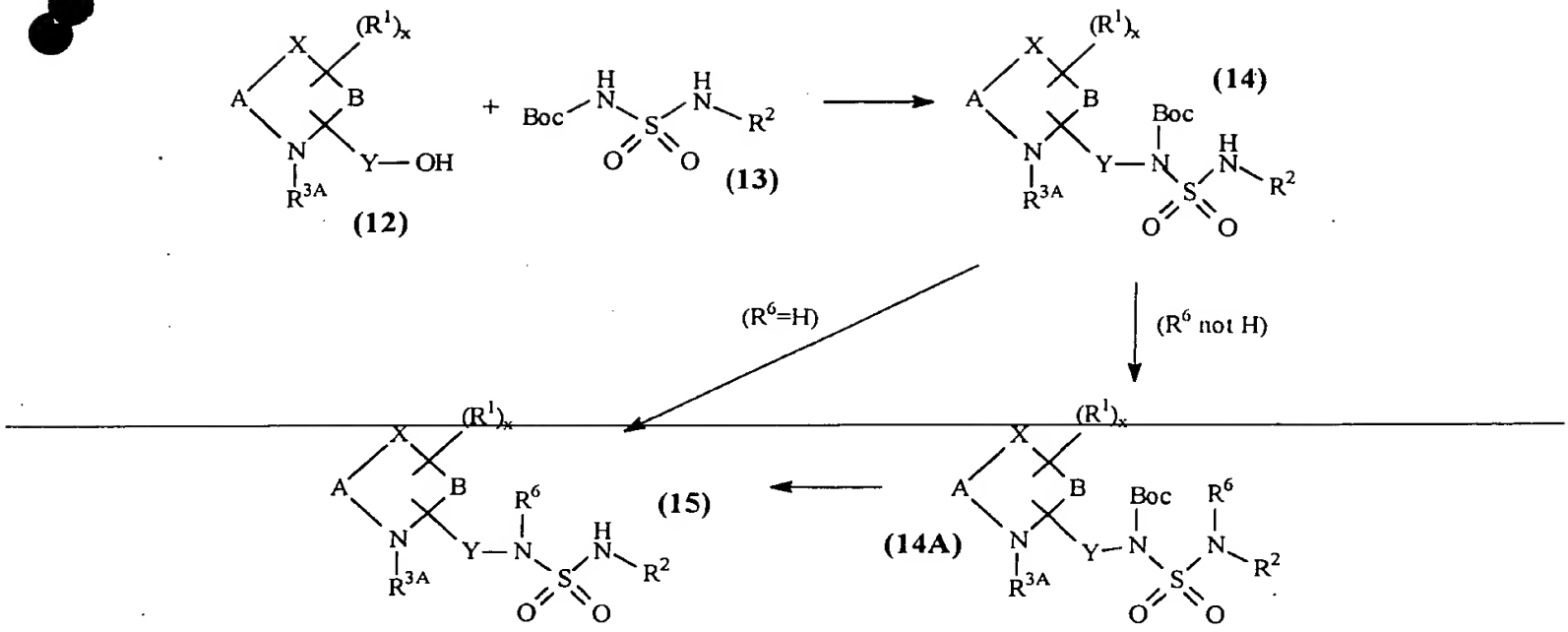


Figure 4

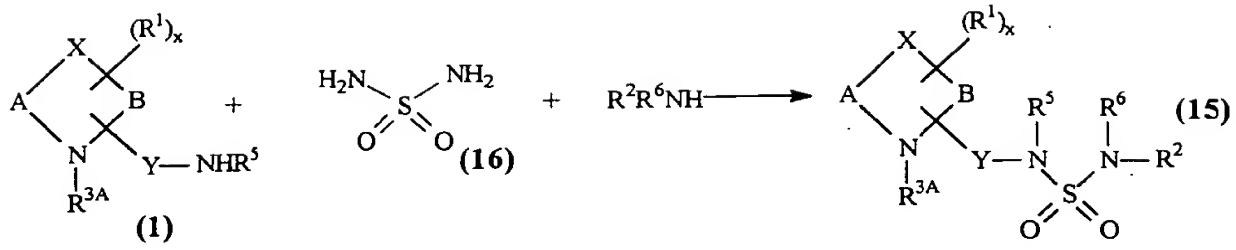


Figure 5

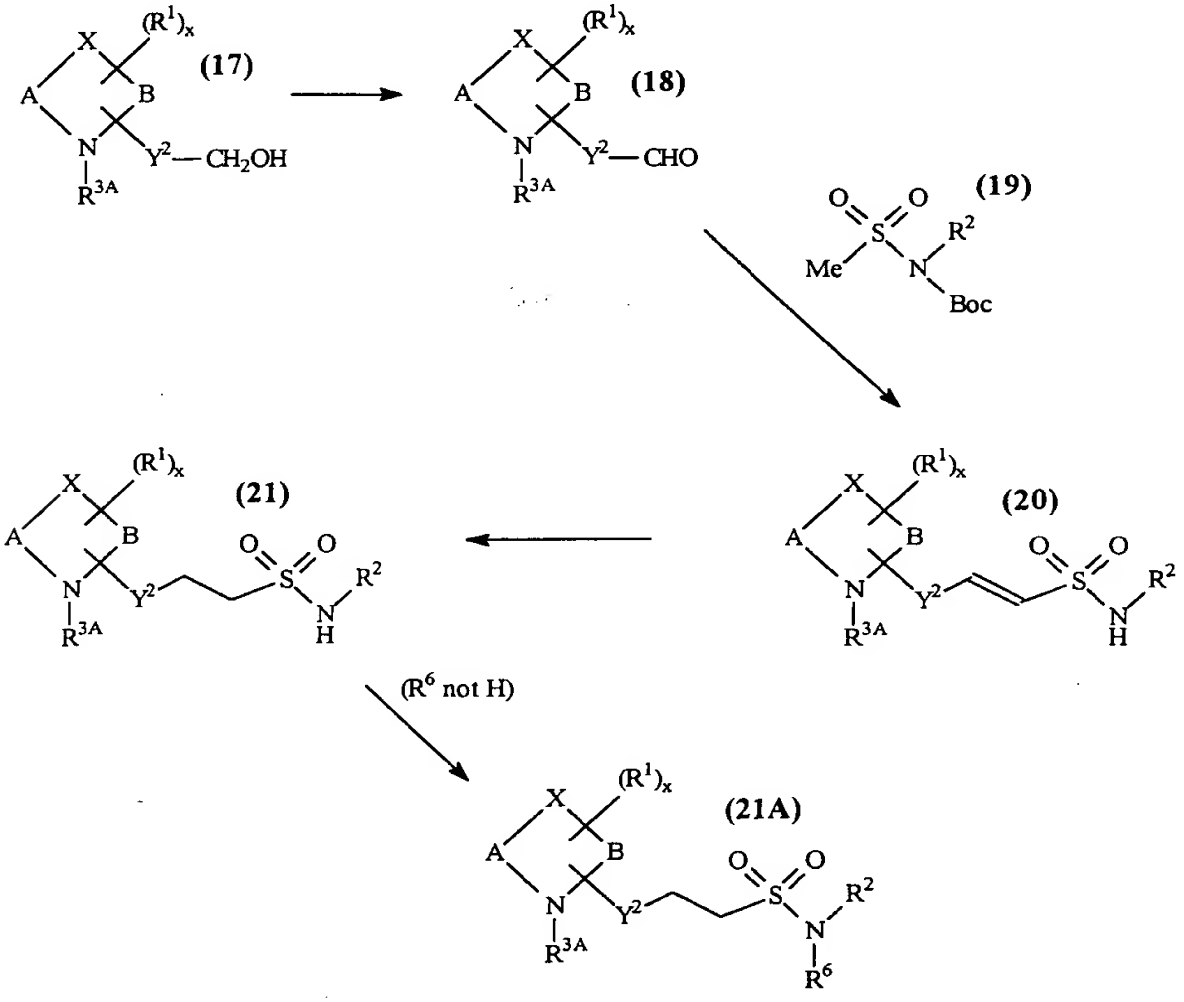


Figure 6

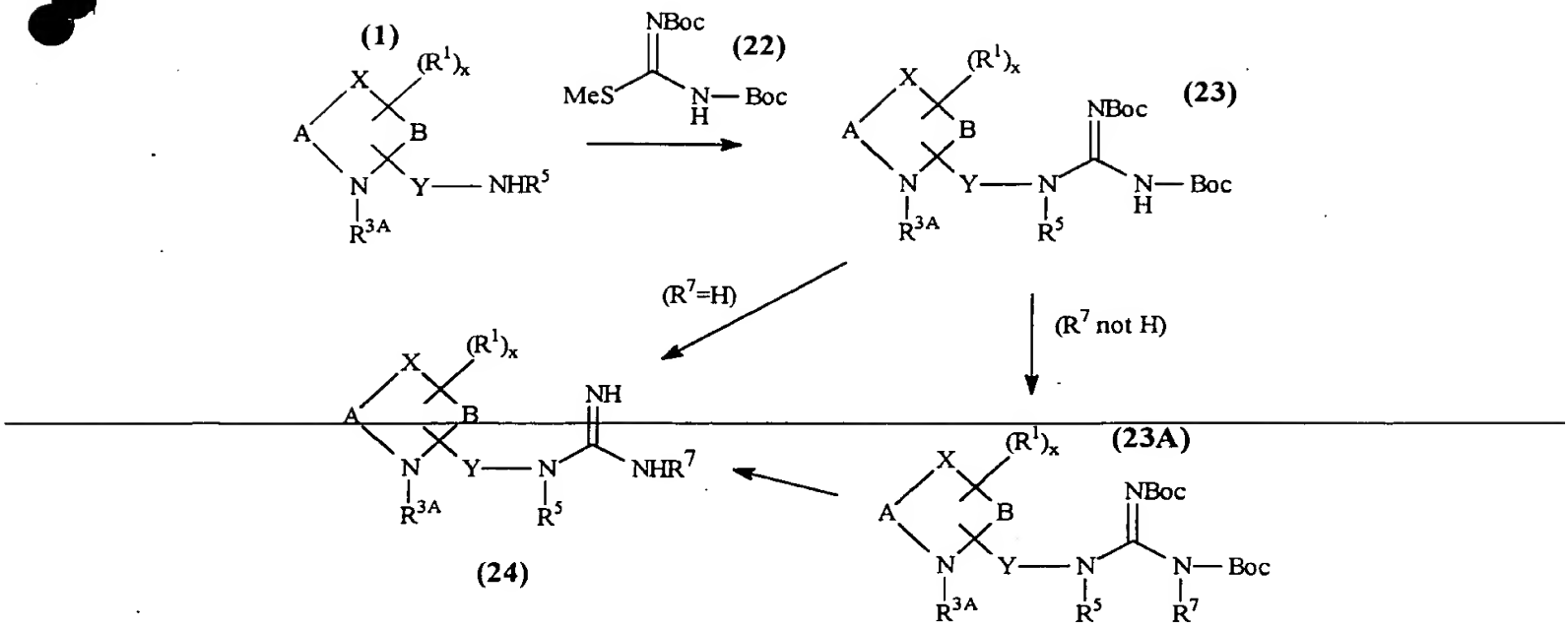


Figure 7

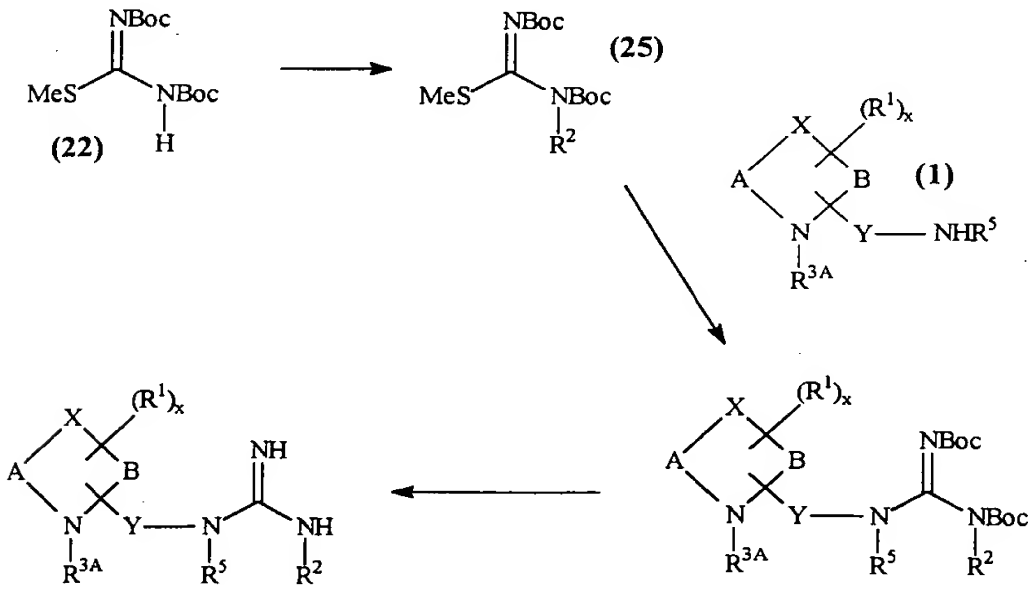


Figure 8

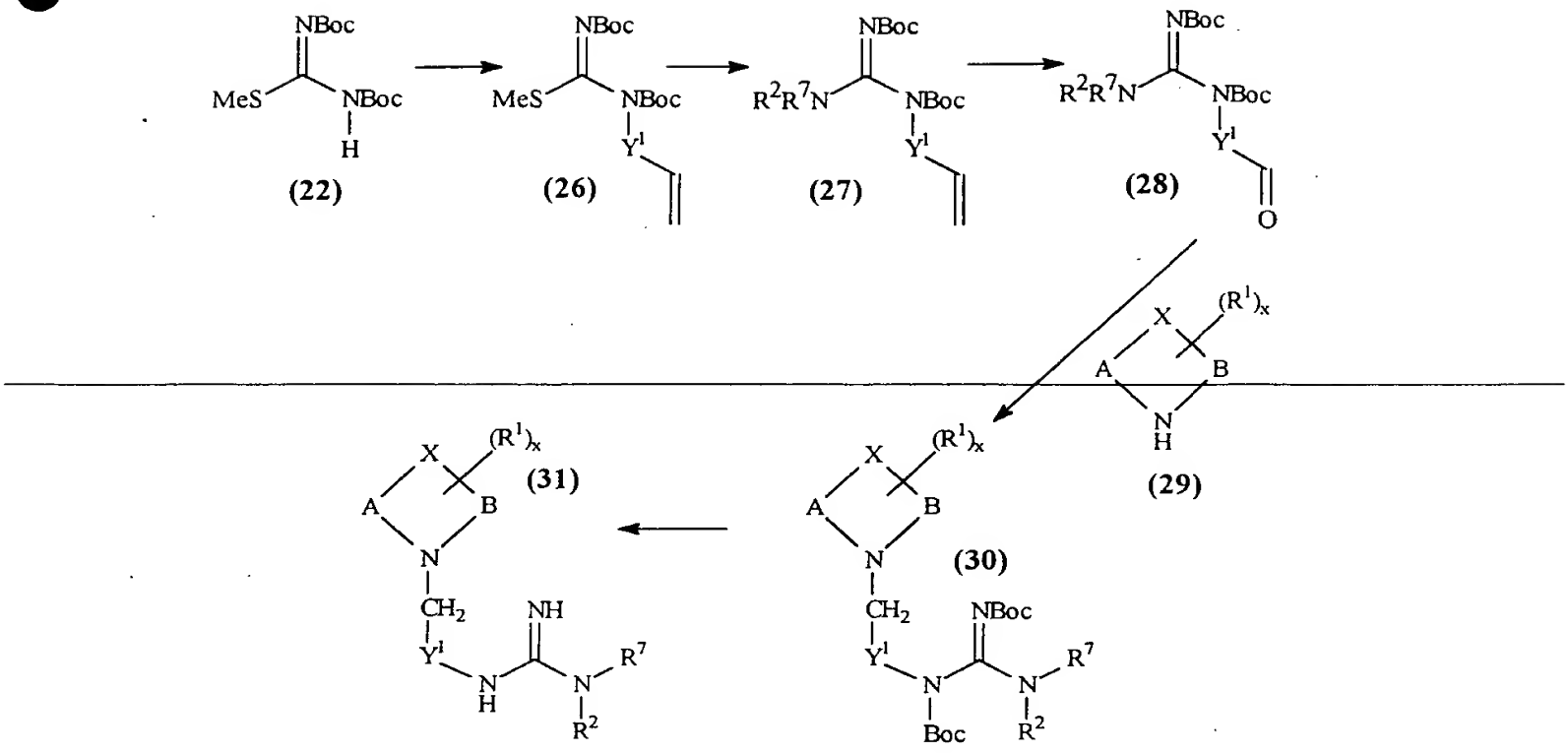


Figure 9

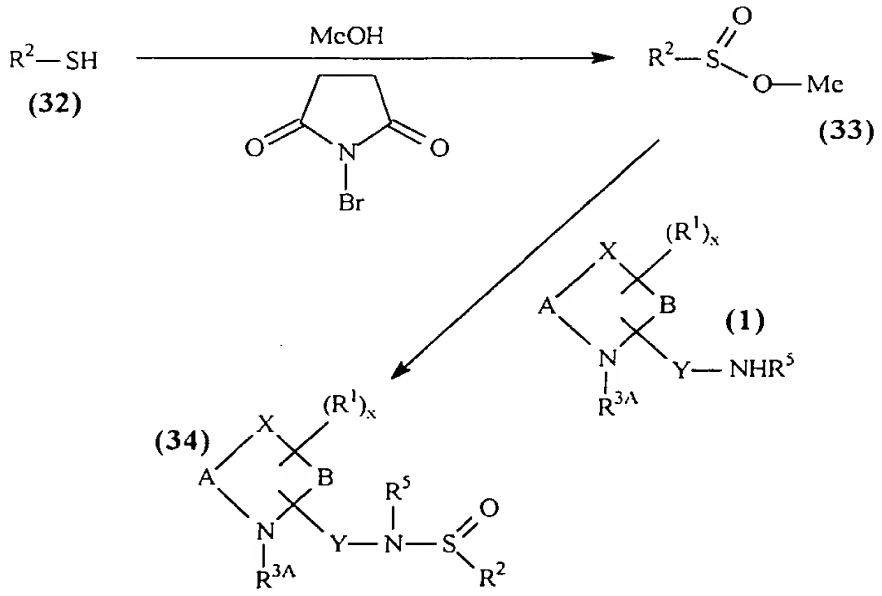


Figure 10

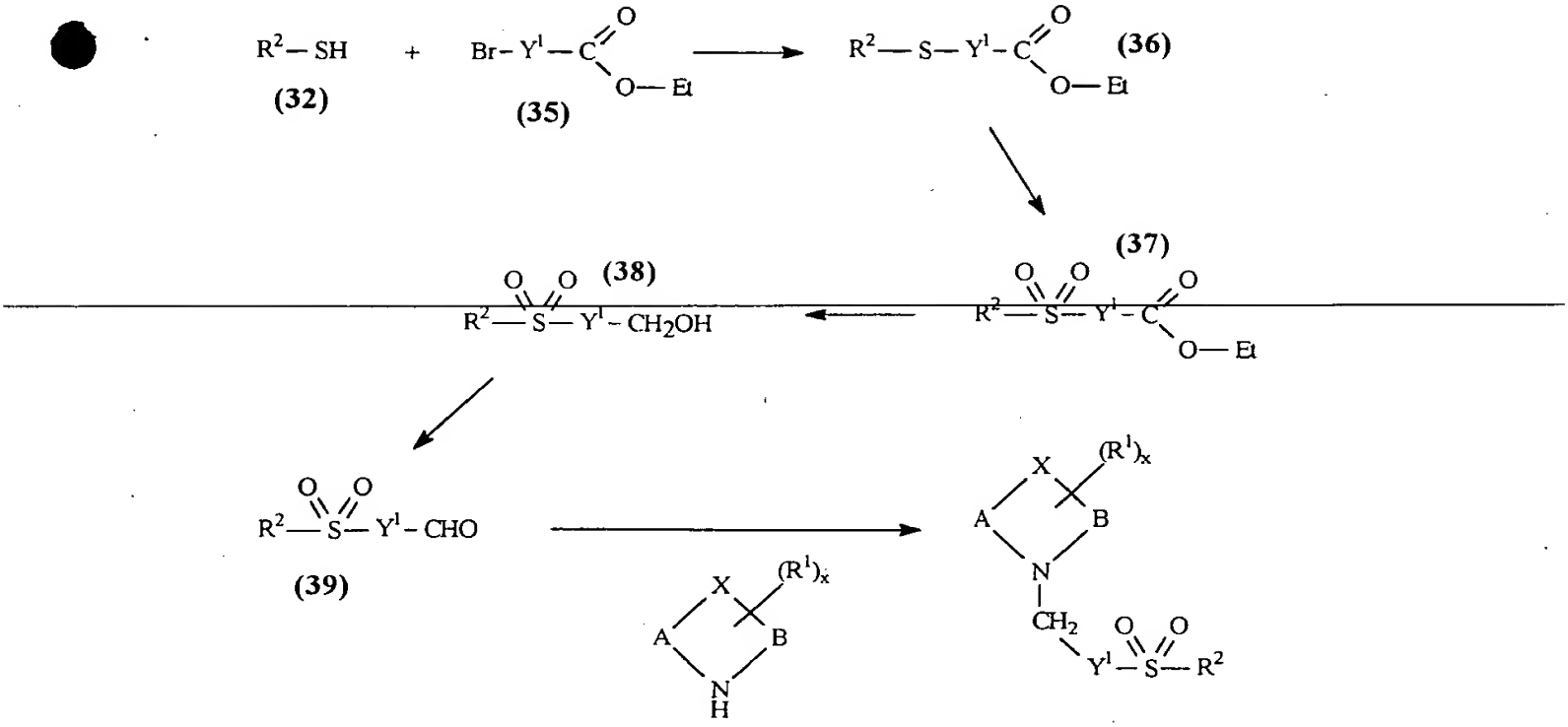


Figure 11

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